

# Articoli Recuperati dalla Query

PUBMED ID: 32982596

DOI: doi.org/10.1016/j.rpor.2020.08.010

Titolo: Hypofractionated radiation therapy with temozolomide versus standard chemoradiation in patients with glioblastoma multiforme (GBM): A prospective, single institution experience.

Autori: Rayan A., Abdel-Kareem S., Hasan H., Zahran AM., Gamal DA.

Data di Pubblicazione: 2020-9-28

Abstract: Our results showed that HFRT with concurrent TMZ is a feasible therapeutic approach in patients with GBM, especially those with poor prognostic factors, assuring high treatment compliance and low toxicity rates. Dose escalation and reduction in overall treatment time are clear advantages of HFRT, while at least the same survival rates as conventional fractionated RT are maintained.

Journal Title: Reports of practical oncology and radiotherapy : journal of Greater Poland Cancer Center in Poznan and Polish Society of Radiation Oncology

PUBMED ID: 32935821

DOI: doi.org/10.6061/clinics/2020/e1553

Titolo: Patterns of recurrence and outcomes of glioblastoma multiforme treated with chemoradiation and adjuvant temozolomide.

Autori: Faustino AC., Viani GA., Hamamura AC.

Data di Pubblicazione: 2020-9-16

Abstract: The median OS of Brazilian patients with GBM treated with RT and TMZ was satisfactory. Although TMZ therapy has become the standard of care for patients with newly diagnosed GBM, the recurrence rate is extremely high. Metronomic TMZ as salvage treatment improved survival in these patients.

Journal Title: Clinics (Sao Paulo, Brazil)

PUBMED ID: 32923898

DOI: doi.org/10.1200/PO.19.00298

Titolo: Outcomes of BRAF V600E Pediatric Gliomas Treated With Targeted BRAF Inhibition.

Autori: Nobre L., Zapotocky M., Ramaswamy V., Ryall S., Bennett J., Alderete D., Balaguer Guill J., Baroni L., Bartels U., Bavle A., Bornhorst M., Boue D R., Canete A., Chintagumpala M., Coven SL., Cruz O., Dahiya S., Dirks P., Dunkel IJ., Eisenstat D., Faure Conter C., Finch E., Finlay JL., Frappaz D., Garre ML., Gauvain K., Bechensteen AG., Hansford JR., Harting I., Hauser P., Hazrati LN., Huang A., Injac SG., Iurilli V., Karajannis M., Kaur G., Kyncl M., Krskova L., Laperriere N., Larouche V., Lassaletta A., Leary S., Lin F., Mascelli S., McKeown T., Milde T., Morales La Madrid A., Morana G., Morse H., Mushtaq N., Osorio DS., Packer R., Pavelka Z., Quiroga-Cantero E., Rutka J., Sabel M., Salgado D., Solano P., Sterba J., Su J., Sumerauer D., Taylor M D., Toledano H., Tsang DS., Valente Fernandes M., van Landeghem F., van Tilburg CM., Wilson B., Witt O., Zamecnik J., Bouffet E., Hawkins C., Tabori U.

Data di Pubblicazione: 2020-9-14

Abstract: Use of BRAF inhibition results in robust and durable responses in BRAF V600E-mutated PLGG. Prospective studies are required to determine long-term survival and functional outcomes with BRAF inhibitor therapy in childhood gliomas.

Journal Title: JCO precision oncology

PUBMED ID: 32917486

DOI: doi.org/10.1016/j.clon.2020.08.011

Titolo: Prospective Longitudinal Assessment of Quality of Life and Activities of Daily Living as Patient-Reported Outcome Measures in Recurrent/Progressive Glioma Treated with High-dose Salvage Re-irradiation.

Autori: Maitre P., Gupta T., Maitre M., Goda J., Krishnatry R., Chatterjee A., Sridhar E., Sahay A., Mokhal S., Moiyadi A., Shetty P., Patil V., Jalali R.

Data di Pubblicazione: 2020-9-12

Abstract: High-dose salvage re-irradiation in carefully selected patients with recurrent/progressive glioma is associated with stable QOL (preserved functional domains and reduced symptom burden) and improvement in ADL (greater functional independence) over time with encouraging survival outcomes.

Journal Title: Clinical oncology (Royal College of Radiologists (Great Britain))

PUBMED ID: 32913543

DOI: Mancante

Titolo: IL13RA2 is overexpressed in malignant gliomas and related to clinical outcome of patients.

Autori: Zeng J., Zhang J., Yang YZ., Wang F., Jiang H., Chen HD., Wu HY., Sai K., Hu WM.

Data di Pubblicazione: 2020-9-11

Abstract: IL13RA2 was high expression in some glioma subtypes, and significantly correlated with poor prognosis. Based on its role in CAR-T therapy, it might act as an extremely important and specific therapeutic target for human malignant gliomas, especially in IDH wild-type LGG, "IDH wild-type and TERT promoter mutated" GBM and H3K27M-mutated diffuse midline glioma, and improve the clinical outcomes of these patients.

Journal Title: American journal of translational research

PUBMED ID: 32883128

DOI: doi.org/10.1177/0300060520951395

Titolo: Anti-PD-1, anti-VEGF, and temozolomide therapy in a patient with recurrent glioblastoma: a case report.

Autori: Chen C., Zuo W., Yang P., Zhang Y.

Data di Pubblicazione: 2020-9-5

Abstract: The experience of this complicated case indicates the possible application of immune checkpoint inhibitors, anti-angiogenesis agents, and cytotoxic reagents for recurrent glioblastoma. The administration of this three-agent regimen appears safe and effective. However, further clinical trials are warranted.

Journal Title: The Journal of international medical research

PUBMED ID: 32859817

DOI: doi.org/10.4103/0028-3886.293441

Titolo: Risk Stratification in Low Grade Glioma: A Single Institutional Experience.

Autori: Keshri V., Deshpande RP., Chandrasekhar YBVK., Panigrahi M., Rao IS., Babu PP.

Data di Pubblicazione: 2020-8-30

Abstract: Taken together, the clinical symptoms, expression of molecular markers and the prognosis details provided by our results can help for better management of LGG cases. We further propose to use following five factors to accurately describe the prognosis and tumor recurrence: 1) Age >50 years, 2) tumor size >5 cm, 3) MIB index >5%, 4) KPS score < 70 and 5) gemistocytic pathology.

Journal Title: Neurology India

PUBMED ID: 32847475

DOI: doi.org/10.1080/0284186X.2020.1778181

Titolo: Longitudinal study of cognitive function in glioma patients treated with modern radiotherapy techniques and standard chemotherapy.

Autori: Rydelius A., Lätt J., Kinhult S., Engelholm S., Van Westen D., Pihlgård M., Bengzon J., Sundgren PC., Lilja Å.

Data di Pubblicazione: 2020-8-28

Abstract: None

Journal Title: Acta oncologica (Stockholm, Sweden)

PUBMED ID: 32823939

DOI: doi.org/10.3390/cancers12082284

Titolo: Multi-Parametric Deep Learning Model for Prediction of Overall Survival after Postoperative Concurrent Chemoradiotherapy in Glioblastoma Patients.

Autori: Yoon HG., Cheon W., Jeong SW., Kim HS., Kim K., Nam H., Han Y., Lim DH.

Data di Pubblicazione: 2020-8-23

Abstract: This study aimed to investigate the performance of a deep learning-based survival-prediction model, which predicts the overall survival (OS) time of glioblastoma patients who have received surgery followed by concurrent chemoradiotherapy (CCRT). The medical records of glioblastoma patients who had received surgery and CCRT between January 2011 and December 2017 were retrospectively reviewed. Based on our inclusion criteria, 118 patients were selected and semi-randomly allocated to training and test datasets (3:1 ratio, respectively). A convolutional neural network-based deep learning model was trained with magnetic resonance imaging (MRI) data and clinical profiles to predict OS. The MRI was reconstructed by using four pulse sequences (22 slices) and nine images were selected based on the longest slice of glioblastoma by a physician for each pulse sequence. The clinical profiles consist of personal, genetic, and treatment factors. The concordance index (C-index) and integrated area under the curve (iAUC) of the time-dependent area-under-the-curve curves of each model were calculated to evaluate the performance of the survival-prediction models. The model that incorporated clinical and radiomic features showed a higher C-index (0.768 (95% confidence interval (CI): 0.759, 0.776)) and iAUC (0.790 (95% CI: 0.783, 0.797)) than the model using clinical features alone (C-index = 0.693 (95% CI: 0.685, 0.701); iAUC = 0.723 (95% CI: 0.716, 0.731)) and the model using radiomic features alone (C-index = 0.590 (95% CI: 0.579, 0.600); iAUC = 0.614 (95% CI: 0.607, 0.621)). These improvements to the C-indexes and iAUCs were validated using the 1000-times bootstrapping method; all were statistically significant.

Journal Title: Cancers

PUBMED ID: 32817593

DOI: doi.org/10.1172/JCI140378

Titolo: Mass cytometry detects H3.3K27M-specific vaccine responses in diffuse midline glioma.

Autori: Mueller S., Taitt JM., Villanueva-Meyer JE., Bonner ER., Nejo T., Lulla RR., Goldman S., Banerjee A., Chi SN., Whipple NS., Crawford JR., Gauthier K., Nazemi KJ., Watchmaker PB., Almeida ND., Okada K., Salazar AM., Gilbert RD., Nazarian J., Molinaro AM., Butterfield LH., Prados MD., Okada H.

Data di Pubblicazione: 2020-8-21

Abstract: Administration of the H3.3K27M-specific vaccine is well tolerated. Patients with H3.3K27M-specific CD8+ immunological responses demonstrated prolonged OS compared to non-responders.

Journal Title: The Journal of clinical investigation

PUBMED ID: 32811600  
DOI: doi.org/10.29271/jcsp.2020.07.713  
Titolo: Prognostic Value of ABO Blood Groups in Patients with Glioblastoma Multiforme.  
Autori: Sokmen FC., Karacin C.  
Data di Pubblicazione: 2020-8-20  
Abstract: An association was detected among ABO blood groups and prognosis in patients with GBM. It was observed that blood groups significantly affected survival and that median survival was significantly shorter in Non-O blood groups when compared blood group O. Key Words: Glioblastoma multiforme, ABO blood group, Prognosis, Survival.  
Journal Title: Journal of the College of Physicians and Surgeons--Pakistan : JCPSP

PUBMED ID: 32793502  
DOI: doi.org/10.3389/fonc.2020.01257  
Titolo: Development of a Nomogram With Alternative Splicing Signatures for Predicting the Prognosis of Glioblastoma: A Study Based on Large-Scale Sequencing Data.  
Autori: Wang Z., Gao L., Guo X., Feng C., Lian W., Deng K., Xing B.  
Data di Pubblicazione: 2020-8-15  
Abstract: None  
Journal Title: Frontiers in oncology

PUBMED ID: 32793489  
DOI: doi.org/10.3389/fonc.2020.01188  
Titolo: Encouraging Clinical Evolution of a Pediatric Patient With Relapsed Diffuse Midline Glioma Who Underwent WT1-Targeting Immunotherapy: A Case Report and Literature Review.  
Autori: Hashii Y., Oka Y., Kagawa N., Hashimoto N., Saitou H., Fukuya S., Kanegae M., Ikejima S., Oji Y., Ozono K., Tsuboi A., Sugiyama H.  
Data di Pubblicazione: 2020-8-15  
Abstract: Diffuse midline glioma (DMG) in children is a highly aggressive, malignant brain tumor that is fatal when relapsed. Wilms tumor 1 (WT1) is a high-priority antigen target for cancer immunotherapy. We hereby report on a pediatric patient who had DMG that regrew after chemoradiotherapy and underwent WT1 peptide vaccination. A 13-year-old Japanese boy presented with vertigo, diplopia, and right hemiplegia at the initial visit to another hospital, where he was diagnosed with DMG by magnetic resonance imaging (MRI); DMG was categorized to histological grade IV glioma. The patient underwent radiotherapy and chemotherapy with temozolomide. After three cycles of chemotherapy, MRI revealed tumor regrowth that translated into deteriorated clinical manifestations. Immunohistochemically, the H3.3K27M mutation in the biopsy specimen was confirmed and the specimen was positive for WT1 protein. The patient underwent WT1-targeting immunotherapy with the WT1-specific peptide vaccine because of having HLA-A  
Journal Title: Frontiers in oncology

PUBMED ID: 32793467  
DOI: doi.org/10.3389/fonc.2020.01057  
Titolo: Prognostic and Predictive Value of a Long Non-coding RNA Signature in Glioma: A lncRNA Expression Analysis.  
Autori: Pan YB., Zhu Y., Zhang QW., Zhang CH., Shao A., Zhang J.  
Data di Pubblicazione: 2020-8-15  
Abstract: The current histologically based grading system for glioma does not accurately predict which patients will have better outcomes or benefit from

m adjuvant chemotherapy. We proposed that combining the expression profiles of multiple long non-coding RNAs (lncRNAs) into a single model could improve prediction accuracy. We included 1,094 glioma patients from three different datasets. Using the least absolute shrinkage and selection operator (LASSO) Cox regression model, we built a multiple-lncRNA-based classifier on the basis of a training set. The predictive and prognostic accuracy of the classifier was validated using an internal test set and two external independent sets. Using this classifier, we classified patients in the training set into high- or low-risk groups with significantly different overall survival (OS, HR = 8.42, 95% CI = 4.99-14.2,  
Journal Title: Frontiers in oncology

PUBMED ID: 32776277

DOI: doi.org/10.1007/s00401-020-02194-y

Titolo: Infratentorial IDH-mutant astrocytoma is a distinct subtype.

Autori: Banan R., Stichel D., Bleck A., Hong B., Lehmann U., Suwala A., Reinhardt A., Schrimpf D., Buslei R., Stadelmann C., Ehlert K., Prinz M., Acker T., Schittenhelm J., Kaul D., Schweizer L., Capper D., Harter PN., Etminan N., Jones DTW., Pfister SM., Herold-Mende C., Wick W., Sahm F., von Deimling A., Hartmann C., Reuss DE.

Data di Pubblicazione: 2020-8-11

Abstract: Diffuse IDH-mutant astrocytic tumors are rarely diagnosed in the cerebellum or brainstem. In this multi-institutional study, we characterized a series of primary infratentorial IDH-mutant astrocytic tumors with respect to clinical and molecular parameters. We report that about 80% of IDH mutations in these tumors are of non-IDH1-R132H variants which are rare in supratentorial astrocytomas. Most frequently, IDH1-R132C/G and IDH2-R172S/G mutations were present. Moreover, the frequencies of ATRX-loss and MGMT promoter methylation, which are typically associated with IDH mutations in supratentorial astrocytic tumors, were significantly lower in the infratentorial compartment. Gene panel sequencing revealed two samples with IDH1-R132C/H3F3A-K27M co-mutations. Genome-wide DNA methylation as well as chromosomal copy number profiling provided further evidence for a molecular distinctiveness of infratentorial IDH-mutant astrocytomas. Clinical outcome of patients with infratentorial IDH-mutant astrocytomas is significantly better than that of patients with diffuse midline gliomas, H3K27M-mutant ( $p < 0.005$ ) and significantly worse than that of patients with supratentorial IDH-mutant astrocytomas ( $p = 0.028$ ). The presented data highlight the very existence and distinctiveness of infratentorial IDH-mutant astrocytomas that have important implications for diagnostics and prognostication. They imply that molecular testing is critical for detection of these tumors, since many of these tumors cannot be identified by immunohistochemistry applied for the mutated IDH1-R132H protein or loss of ATRX.

Journal Title: Acta neuropathologica

PUBMED ID: 32727404

DOI: doi.org/10.1186/s12885-020-07211-7

Titolo: Multiple formin proteins participate in glioblastoma migration.

Autori: Heuser VD., Kiviniemi A., Lehtinen L., Munthe S., Kristensen BW., Posti JP., Sipilä JOT., Vuorinen V., Carpén O., Gardberg M.

Data di Pubblicazione: 2020-7-31

Abstract: Formins FHOD1 and INF2 participate in glioblastoma cell migration. Moderate/high expression of INF2 in glioblastoma tissue is associated with worse outcome. Taken together, our in vitro and tissue studies suggest a pivotal role for INF2 in glioblastoma. When specific inhibiting compounds become available, INF2 could be a target in the search for novel glioblastoma therapies.

Journal Title: BMC cancer

PUBMED ID: 32721125

DOI: doi.org/10.1002/cnr2.1216

Titolo: Current clinical management of patients with glioblastoma.

Autori: Lowe S., Bhat KP., Olar A.

Data di Pubblicazione: 2020-7-29

Abstract: GB is an extremely complex disease, and despite recent progress and advanced therapeutic strategies, the overall patient's prognosis remains dismal. Innovative strategies and integrative ways of approach to disease are urgently needed.

Journal Title: Cancer reports (Hoboken, N.J.)

PUBMED ID: 32680476

DOI: doi.org/10.1186/s12885-020-07153-0

Titolo: The predominant expression of cancer stem cell marker ALDH1A3 in tumor infiltrative area is associated with shorter overall survival of human glioblastoma.

Autori: Gan C., Pierscianek D., El Hindy N., Ahmadipour Y., Keyvani K., Sure U., Zhu Y.

Data di Pubblicazione: 2020-7-19

Abstract: Inter- and intra-tumoral heterogeneous expression of ALDH1A3 was exhibited in GBMs. A high immunoreactivity of ALDH1A3 in tumor infiltrative area was associated with shorter OS, especially in patients with MGMT promoter methylation. Our findings propose ALDH1A3 not only as a predictive biomarker but also as a potential target for personalized therapy of GBM.

Journal Title: BMC cancer

PUBMED ID: 32674977

DOI: doi.org/10.1016/j.jgo.2020.07.001

Titolo: Chemotherapy toxicities and geriatric syndromes in older patients with malignant gliomas.

Autori: Wasilewski A., Alam A., Mohile N.

Data di Pubblicazione: 2020-7-18

Abstract: Older patients with MG experience significant polypharmacy, treatment toxicities and falls. Studies incorporating geriatric assessment tools may better determine associations between geriatric syndromes and survival. Clinical trials in older patients should also include non-survival outcomes.

Journal Title: Journal of geriatric oncology

PUBMED ID: 32664146

DOI: doi.org/10.1097/MD.00000000000021147

Titolo: Effect of valproic acid on overall survival in patients with high-grade gliomas undergoing temozolomide: A nationwide population-based cohort study in Taiwan.

Autori: Kuo YJ., Yang YH., Lee IY., Chen PC., Yang JT., Wang TC., Lin MH., Yang WH., Cheng CY., Chen KT., Huang WC., Lee MH.

Data di Pubblicazione: 2020-7-16

Abstract: High-grade gliomas (HGGs) are a rapidly progressive and highly recurrent group of primary brain tumors. Despite aggressive surgical resection with chemoradiotherapy, prognoses remained poor. Valproic acid (VPA), a histone deacetylase inhibitor has shown the potential to inhibit glioma cell growth in vitro through several diverse mechanisms. However clinical studies regarding the effect of VPA on HGGs are limited. This study aimed to investigate whether using VPA in patients with HGGs under temozolomide (TMZ) would lead to a better overall survival (OS). We used the Taiwan National Health Insurance

rance Research database to conduct this population-based cohort study. A total of 2379 patients with HGGs under TMZ treatment were included and were further classified into VPA (n=1212, VPA  $\geq$  84 defined daily dose [DDD]) and non-VPA (n=1167, VPA < 84 DDD) groups. Each patient was followed from 1998 to 2013 or until death. A Cox proportional hazard regression was performed to evaluate the effect of VPA and OS. The VPA group had a longer mean OS time compared with the non-VPA group (OS: 50.3 $\pm$ 41.0 vs 42.0 $\pm$ 37.2 months, P<.001). In patients between 18 and 40 years old, the difference is most significant (OS: 70.5 $\pm$ 48.7 vs 55.1 $\pm$ 46.0, P=.001). The adjusted hazard ratio is 0.81 (95% confidence interval, 0.72-0.91) for the VPA group relative to the non-VPA group. VPA at over 84 DDD improved OS in HGGs TMZ treatment.

Journal Title: Medicine

PUBMED ID: 32649812

DOI: doi.org/10.17116/neiro20208403135

Titolo: [Glioblastomas in patients with medulloblastomas after combined treatment].

Autori: Golanov AV., Ryzhova MV., Trunin YY., Zheludkova OG., Antipina NA., Cherkesov IV.

Data di Pubblicazione: 2020-7-11

Abstract: Medulloblastoma (MB) is the most common brain malignancy in children occurring in the posterior cranial fossa. This tumor is characterized by high risk of metastasis along the CSF pathways. Significant progress in research of this tumor and appropriate treatment is associated with determining the various molecular categories of primary medulloblastomas. This analysis includes certain factors of cytogenetic and transcriptional proliferation. Modern treatment approaches for patients older than 3 years include advanced resection, craniospinal irradiation with a boost on the postoperative bed followed by platinum-based chemotherapy. Conventional radiotherapy including craniospinal irradiation results a significant number of complications. Morbidity rate is increased throughout long-term follow-up. Secondary tumors including glioblastomas are under special attention since their occurrence is associated with a fatal outcome. This may partially explain the fact that chemotherapy without repeated morphological verification doesn't always ensure tumor growth control in patients with recurrent medulloblastomas. The authors consider irradiation-induced glioblastomas secondary to primarily verified medulloblastomas in patients who had previously undergone craniospinal irradiation as a component of combined treatment after tumor resection. It was found that the incidence of this phenomenon is significant and made up about 10% among patients with recurrent medulloblastomas. This value is significantly higher compared to previous data. The authors analyzed patterns of occurrence of irradiation-induced glioblastomas depending on the molecular genetic group and clinical characteristics of patients after primary surgery. Treatment outcomes were estimated too. It was concluded that morphological verification is necessary if long-term recurrence is diagnosed after combined treatment of medulloblastoma.

Journal Title: Zhurnal voprosy neirokhirurgii imeni N. N. Burdenko

PUBMED ID: 32648211

DOI: doi.org/10.1007/s12253-020-00868-2

Titolo: Low Fraction Size Re-irradiation for Large Volume Recurrence of Glioma Tumours.

Autori: Dobi Á., Darázs B., Fodor E., Cserhádi A., Együd Z., Maráz A., László S., Dodd L., Reisz Z., Barzó P., Oláh J., Hideghéty K.

Data di Pubblicazione: 2020-7-11

Abstract: The aim of the present study was to evaluate the efficacy of re-irradiation (re-RT) in patients with advanced local relapses of glial tumours

and to define the factors influencing the result of the hyper-fractionated external beam therapy on progression after primary management. We have analysed the data of 55 patients with brain tumours (GBM: 28) on progression, who were re-irradiated between January 2007 and December 2018. The mean volume of the recurrent tumour was 118 cm

Journal Title: Pathology oncology research : POR

PUBMED ID: 32642720

DOI: doi.org/10.1093/noajnl/vdz052

Titolo: Phase I trial of dimethyl fumarate, temozolomide, and radiation therapy in glioblastoma.

Autori: Shafer D., Tombes MB., Shrader E., Ryan A., Bandyopadhyay D., Dent P., Malkin M.

Data di Pubblicazione: 2020-7-10

Abstract: DMF may be safely combined with RT and TMZ in patients with newly diagnosed GBM. The RP2D for DMF is 240 mg three times daily.

Journal Title: Neuro-oncology advances

PUBMED ID: 32642703

DOI: doi.org/10.1093/noajnl/vdaa050

Titolo: Value of [

Autori: Graham MS., Krebs S., Bale T., Domfe K., Lobaugh SM., Zhang Z., Dunphy MP., Kaley T., Young RJ.

Data di Pubblicazione: 2020-7-10

Abstract: FDG PET is a promising imaging tool to further stratify prognosis in recurrent GBM patients on antiangiogenic therapy.

Journal Title: Neuro-oncology advances

PUBMED ID: 32642664

DOI: doi.org/10.1093/noajnl/vdz033

Titolo: Constitutional mismatch repair deficiency-associated brain tumors: report from the European C4CMMRD consortium.

Autori: Guerrini-Rousseau L., Varlet P., Colas C., Andreiuolo F., Bourdeaut F., Dahan K., Devalck C., Faure-Contier C., Genuardi M., Goldberg Y., Kühlen M., Moalla S., Opocher E., Perez-Alonso V., Sehested A., Slavc I., Unger S., Wimmer K., Grill J., Brugières L.

Data di Pubblicazione: 2020-7-10

Abstract: Several characteristics could help suspecting CMMRD in pediatric malignant BTs: giant cells on histology, previous malignancies, parental consanguinity, café-au-lait macules, multiple BTs, and developmental brain anomalies. The prognosis of CMMRD-associated BT treated with standard therapies is poor requiring new therapeutic up-front approaches.

Journal Title: Neuro-oncology advances

PUBMED ID: 32582531

DOI: doi.org/10.3389/fonc.2020.00747

Titolo: None

Autori: Berberich A., Bartels F., Tang Z., Knoll M., Pusch S., Hücke N., Kessler T., Dong Z., Wiestler B., Winkler F., Platten M., Wick W., Abdollahi A., Lemke D.

Data di Pubblicazione: 2020-6-26

Abstract: None

Journal Title: Frontiers in oncology

PUBMED ID: 32557428



DOI: doi.org/10.4414/smw.2020.20256

Titolo: A contemporary perspective on the diagnosis and treatment of diffuse gliomas in adults.

Autori: Roth P., Hottinger AF., Hundsberger T., Läubli H., Schucht P., Reine rt M., Mamot C., Roelcke U., Pesce G., Hofer S., Weller M.

Data di Pubblicazione: 2020-6-20

Abstract: Gliomas are intrinsic brain tumours, which are classified by the World Health Organization (WHO) into different grades of malignancy, with glioblastoma being the most frequent and most malignant subtype (WHO grade IV). Mutations in the isocitrate dehydrogenase (IDH) 1 or 2 genes are frequent in lower (WHO II/III) grade tumours but typically absent in classical glioblastoma. IDH mutations are associated with a better prognosis compared with IDH wild-type tumours of the same WHO grade. Following detection of a tumour mass by imaging, maximum safe surgery as feasible is commonly performed to reduce mass effect and to obtain tissue allowing histopathological diagnosis and molecular assessment. Radiotherapy has been the mainstay in the treatment of diffuse gliomas for several decades. It provides improved local control, but is not curative. Furthermore, several randomised trials have shown that the addition of alkylating chemotherapy, either temozolomide or nitrosourea-based regimens, to radiotherapy results in prolonged survival. Tumour-treating fields (TTFields) have emerged as an additional treatment option in combination with maintenance temozolomide treatment for patients with newly diagnosed glioblastoma. Treatment at recurrence is less standardised and depends on the patient's performance status, symptom burden and prior treatments. Bevacizumab prolongs progression-free survival in newly diagnosed and recurrent glioblastoma, but does not impact overall survival. However, in Switzerland and some other countries, it is still considered a valuable treatment option to reduce clinical symptom burden. Given the generally poor outcome for these patients, various novel treatment approaches are currently being explored within clinical trials including immunotherapeutic strategies such as immune checkpoint inhibition and the brain-penetrant proteasome inhibitor marizomib.

Journal Title: Swiss medical weekly

PUBMED ID: 32556862

DOI: doi.org/10.1007/s11060-020-03558-w

Titolo: Children with DIPG and high-grade glioma treated with temozolomide, irinotecan, and bevacizumab: the Seattle Children's Hospital experience.

Autori: Crotty EE., Leary SES., Geyer JR., Olson JM., Millard NE., Sato AA., Ermoian RP., Cole BL., Lockwood CM., Paulson VA., Browd SR., Ellenbogen RG., Hauptman JS., Lee A., Ojemann JG., Vitanza NA.

Data di Pubblicazione: 2020-6-20

Abstract: Our single-center experience demonstrates tolerability of this 3-drug regimen, with prolonged survival in DIPG compared to historical single-agent temozolomide. pHGG survival was comparable to analogous 3-drug regimens and superior to historical agents; however, cure was rare. Children with pHGG remain excellent candidates for the study of novel therapeutics combined with standard therapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 32546647

DOI: doi.org/10.1158/1078-0432.CCR-19-3874

Titolo: Advanced Age Increases Immunosuppression in the Brain and Decreases Immunotherapeutic Efficacy in Subjects with Glioblastoma.

Autori: Ladomersky E., Zhai L., Lauing KL., Bell A., Xu J., Kocherginsky M., Zhang B., Wu JD., Podojil JR., Plataniias LC., Mochizuki AY., Prins RM., Kuntehekar P., Raizer JJ., Dixit K., Lukas RV., Horbinski C., Wei M., Zhou C., Pawelec G., Campisi J., Grohmann U., Prendergast GC., Munn DH., Wainwright DA.

Data di Pubblicazione: 2020-6-18

Abstract: Immunosuppression increases in the brain during advanced age and inhibits antiglioma immunity in older adults. Going forward, it will be important to fully understand the factors and mechanisms in the elderly brain that contribute to the decreased survival of older patients with GBM during treatment with ICB.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 32543245

DOI: doi.org/10.1080/14737175.2020.1775584

Titolo: Improving long-term survival in diffuse intrinsic pontine glioma.

Autori: Felker J., Broniscer A.

Data di Pubblicazione: 2020-6-17

Abstract: The authors propose four main opportunities to improve long-term survival. First, patients should be enrolled in scientifically sound clinical trials that include molecularly profiling either via stereotactic biopsy or liquid biopsy. Second, clinical trials should include more innovative endpoints other than traditional EFS and OS such as MRI/PET imaging findings combined with surrogates of activity (e.g. serial liquid biopsies) to better ascertain biologically active treatments. Third, innovative clinical trial approaches are needed to help allow for the rapid development of combination therapies to be tested. Finally, effort should be concentrated on reversing the effects of the histone mutation, as this malfunctioning development program seems to be key to DIPG relentlessness.

Journal Title: Expert review of neurotherapeutics

PUBMED ID: 32518098

DOI: doi.org/10.1158/1078-0432.CCR-19-4055

Titolo: Phosphorylated Acetyl-CoA Carboxylase Is Associated with Clinical Benefit with Regorafenib in Relapsed Glioblastoma: REGOMA Trial Biomarker Analysis.

Autori: Indraccolo S., De Salvo GL., Verza M., Caccese M., Esposito G., Piga I., Del Bianco P., Pizzi M., Gardiman MP., Eoli M., Rudà R., Brandes AA., Ibrahim T., Rizzato S., Lolli I., Zagonel V., Lombardi G.

Data di Pubblicazione: 2020-6-11

Abstract: We found that AMPK pathway activation is associated with clinical benefit from treatment with regorafenib in relapsed GBM.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 32506137

DOI: doi.org/10.1093/neuonc/noaa140

Titolo: MR Imaging features of Diffuse Intrinsic Pontine Glioma (DIPG) and Relationship to Overall Survival: Report from the International DIPG Registry .

Autori: Leach JL., Roebker J., Schafer A., Baugh J., Chaney B., Fuller C., Fouladi M., Lane A., Doughman R., Drissi R., DeWire-Schottmiller M., Ziegler DS., Minturn JE., Hansford JR., Wang SS., Monje-Deisseroth M., Fisher PG., Gottardo NG., Dholaria H., Packer R., Warren K., Leary SES., Goldman S., Bartels U., Hawkins C., Jones BV.

Data di Pubblicazione: 2020-6-8

Abstract: Baseline imaging features are assessed in the IDIPGR. There was a 9.5% discordance in DIPG diagnosis between local and central review demonstrating need for central imaging confirmation for prospective trials. Although several imaging features were significantly associated with OS (univariable) only age and distant disease were significant on multivariable analyses. The

re was limited association of imaging features with histone mutation status although numbers are small and evaluation exploratory.  
Journal Title: Neuro-oncology

PUBMED ID: 32502459

DOI: doi.org/10.1016/S1470-2045(20)30166-2

Titolo: Response assessment in diffuse intrinsic pontine glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group.

Autori: Cooney TM., Cohen KJ., Guimaraes CV., Dhall G., Leach J., Massimino M., Erbetta A., Chiapparini L., Malbari F., Kramer K., Pollack IF., Baxter P., Laughlin S., Patay Z., Young Poussaint T., Warren KE.

Data di Pubblicazione: 2020-6-6

Abstract: Optimising the conduct of clinical trials for diffuse intrinsic pontine glioma involves use of consistent, objective disease assessments and standardised response criteria. The Response Assessment in Pediatric Neuro-Oncology working group, consisting of an international panel of paediatric and adult neuro-oncologists, clinicians, radiologists, radiation oncologists, and neurosurgeons, was established to address issues and unique challenges in assessing response in children with CNS tumours. A working group was formed specifically to address response assessment in children and young adults with diffuse intrinsic pontine glioma and to develop a consensus on recommendations for response assessment. Response should be assessed using MRI of brain and spine, neurological examination, and anti-inflammatory or antiangiogenic drugs. Clinical imaging standards are defined. As with previous consensus recommendations, these recommendations will need to be validated in prospective clinical trials.

Journal Title: The Lancet. Oncology

PUBMED ID: 32452588

DOI: doi.org/10.1634/theoncologist.2020-0440

Titolo: A Phase II, Single-Arm, Open-Label, Bayesian Adaptive Efficacy and Safety Study of PBI-05204 in Patients with Stage IV Metastatic Pancreatic Adenocarcinoma.

Autori: Roth MT., Cardin DB., Borazanci EH., Steinbach M., Picozzi VJ., Rosemury A., Wadlow RC., Newman RA., Berlin J.

Data di Pubblicazione: 2020-5-27

Abstract: PBI-05204 did not meet its primary endpoint for OS in this study. Recent preclinical data indicate a role for PBI-05204 against glioblastoma multiforme when combined with chemotherapy and radiotherapy. A randomized phase II trial is currently being designed.

Journal Title: The oncologist

PUBMED ID: 32450499

DOI: doi.org/10.1016/j.clineuro.2020.105888

Titolo: Long term follow-up and outcomes in adult patients with thalamic gliomas.

Autori: Li Z., Wu H., Wu B., Lyu J., Liu Y., Tang C., Hua W., Hu S., Wang Y., Zhang Y.

Data di Pubblicazione: 2020-5-26

Abstract: The OS and PFS of adult patients with thalamic glioma were not significantly different between patients in the surgical group and in the IMRT group. IMRT might be an acceptable alternative to surgery for adult patients with unresectable thalamic glioma.

Journal Title: Clinical neurology and neurosurgery

PUBMED ID: 32438648  
DOI: doi.org/10.3390/medicines7050029  
Titolo: Addition of Multimodal Immunotherapy to Combination Treatment Strategies for Children with DIPG: A Single Institution Experience.  
Autori: Van Gool SW., Makalowski J., Bonner ER., Feyen O., Domogalla MP., Pr ix L., Schirmacher V., Nazarian J., Stuecker W.  
Data di Pubblicazione: 2020-5-23  
Abstract: None  
Journal Title: Medicines (Basel, Switzerland)

PUBMED ID: 32392361  
DOI: doi.org/10.1002/1878-0261.12707  
Titolo: Classification of diffuse lower-grade glioma based on immunological profiling.  
Autori: Wu F., Wang ZL., Wang KY., Li GZ., Chai RC., Liu YQ., Jiang HY., Zha i Y., Feng YM., Zhao Z., Zhang W.  
Data di Pubblicazione: 2020-5-12  
Abstract: Transcriptomic data derived from bulk sequencing have been applied to delineate the tumor microenvironment (TME) and define immune subtypes in various cancers, which may facilitate the design of immunotherapy treatment strategies. We herein gathered published gene expression data from diffuse l ower-grade glioma (LGG) patients to identify immune subtypes. Based on the i mmune gene profiles of 402 LGG patients from The Cancer Genome Atlas, we per formed consensus clustering to determine robust clusters of patients, and ev aluated their reproducibility in three Chinese Glioma Genome Atlas cohorts. We further integrated immunogenomics methods to characterize the immune envi ronment of each subtype. Our analysis identified and validated three immune subtypes-Im1, Im2, and Im3-characterized by differences in lymphocyte signat ures, somatic DNA alterations, and clinical outcomes. Im1 had a higher infil tration of CD8+ T cells, Th17, and mast cells. Im2 was defined by elevated c ytolytic activity, exhausted CD8+ T cells, macrophages, higher levels of ane uploidy, and tumor mutation burden, and these patients had worst outcome. Im 3 displayed more prominent T helper cell and APC coinhibition signatures, wi th elevated pDCs and macrophages. Each subtype was associated with distinct somatic alterations. Moreover, we applied graph structure learning-based dim ensionality reduction to the immune landscape and revealed significant intra cluster heterogeneity with Im2 subtype. Finally, we developed and validated an immune signature with better performance of prognosis prediction. Our res ults demonstrated the immunological heterogeneity within diffuse LGG and pro vided valuable stratification for the design of future immunotherapy.  
Journal Title: Molecular oncology

PUBMED ID: 32384274  
DOI: doi.org/10.3171/2020.2.JNS192767  
Titolo: Extent of resection, molecular signature, and survival in 1p19q-code leted gliomas.  
Autori: Garton ALA., Kinslow CJ., Rae AI., Mehta A., Pannullo SC., Magge RS. , Ramakrishna R., McKhann GM., Sisti MB., Bruce JN., Canoll P., Cheng SK., S onabend AM., Wang TJC.  
Data di Pubblicazione: 2020-5-9  
Abstract: By using the NCDB, the authors have demonstrated a side-by-side co mparison of the survival benefits of greater EOR in 1p/19q-codeleted gliomas .  
Journal Title: Journal of neurosurgery

PUBMED ID: 32341580  
DOI: doi.org/10.1038/s41591-020-0827-2

Titolo: Locoregional delivery of CAR T cells to the cerebrospinal fluid for treatment of metastatic medulloblastoma and ependymoma.

Autori: Donovan LK., Delaidelli A., Joseph SK., Bielałowicz K., Fousek K., H olgado BL., Manno A., Srikanthan D., Gad AZ., Van Ommeren R., Przelicki D., Richman C., Ramaswamy V., Daniels C., Pallota JG., Douglas T., Joynt ACM., H aapasalo J., Nor C., Vladoiu MC., Kuzan-Fischer CM., Garzia L., Mack SC., Va radharajan S., Baker ML., Hendrikse L., Ly M., Kharas K., Balin P., Wu X., Q in L., Huang N., Stucklin AG., Morrissy AS., Cavalli FMG., Luu B., Suarez R. , De Antonellis P., Michealraj A., Rastan A., Hegde M., Komosa M., Sirbu O., Kumar SA., Abdullaev Z., Faria CC., Yip S., Hukin J., Tabori U., Hawkins C., Aldape K., Daugaard M., Maris JM., Sorensen PH., Ahmed N., Taylor MD.

Data di Pubblicazione: 2020-4-29

Abstract: Recurrent medulloblastoma and ependymoma are universally lethal, w ith no approved targeted therapies and few candidates presently under clinic al evaluation. Nearly all recurrent medulloblastomas and posterior fossa gro up A (PFA) ependymomas are located adjacent to and bathed by the cerebrospin al fluid, presenting an opportunity for locoregional therapy, bypassing the blood-brain barrier. We identify three cell-surface targets, EPHA2, HER2 and interleukin 13 receptor  $\alpha 2$ , expressed on medulloblastomas and ependymomas, b ut not expressed in the normal developing brain. We validate intrathecal del ivery of EPHA2, HER2 and interleukin 13 receptor  $\alpha 2$  chimeric antigen recepto r T cells as an effective treatment for primary, metastatic and recurrent gr oup 3 medulloblastoma and PFA ependymoma xenografts in mouse models. Finally , we demonstrate that administration of these chimeric antigen receptor T ce lls into the cerebrospinal fluid, alone or in combination with azacytidine, is a highly effective therapy for multiple metastatic mouse models of group 3 medulloblastoma and PFA ependymoma, thereby providing a rationale for clin ical trials of these approaches in humans.

Journal Title: Nature medicine

PUBMED ID: 32340318

DOI: doi.org/10.3390/diagnostics10040247

Titolo: Magnetic Resonance Imaging Derived Biomarkers of IDH Mutation Status and Overall Survival in Grade III Astrocytomas.

Autori: Feraco P., Bacci A., Ferrazza P., van den Hauwe L., Pertile R., Girl ando S., Barbareschi M., Gagliardo C., Morganti AG., Petralia B.

Data di Pubblicazione: 2020-4-29

Abstract: The evaluation of the isocitrate dehydrogenase (IDH) mutation stat us in the glioma decision-making process has diagnostic, prognostic and ther apeutic implications. The aim of this study was to evaluate whether conventi onal magnetic resonance imaging (MRI) and apparent diffusion coefficient (AD C) can noninvasively predict the most common IDH mutational status (R132H) i n GIII-astrocytomas and the overall survival (OS). Hence, twenty-two patient s (9-F, 13-M) with a histological diagnosis of GIII-astrocytoma and evaluati on of IDH-mutation status (12-wild type, 10-mutant) were retrospectively eva luated. Imaging studies were reviewed for the morphological feature and mean ADC values (ADC<sub>m</sub>). Statistics included a Fisher's exact test, Student's

Journal Title: Diagnostics (Basel, Switzerland)

PUBMED ID: 32303840

DOI: doi.org/10.1007/s00401-020-02155-5

Titolo: Pediatric bithalamic gliomas have a distinct epigenetic signature and frequent EGFR exon 20 insertions resulting in potential sensitivity to tar geted kinase inhibition.

Autori: Mondal G., Lee JC., Ravindranathan A., Villanueva-Meyer JE., Tran QT ., Allen SJ., Barreto J., Gupta R., Doo P., Van Ziffle J., Onodera C., Devin e P., Grenert JP., Samuel D., Li R., Metrock LK., Jin LW., Antony R., Alasha ri M., Cheshier S., Whipple NS., Bruggers C., Raffel C., Gupta N., Kline CN.

, Reddy A., Banerjee A., Hall MD., Mehta MP., Khatib Z., Maher OM., Brathwaite C., Pekmezci M., Phillips JJ., Bollen AW., Tihan T., Lucas JT., Broniscer A., Berger MS., Perry A., Orr BA., Solomon DA.

Data di Pubblicazione: 2020-4-19

Abstract: Brain tumors are the most common solid tumors of childhood, and the genetic drivers and optimal therapeutic strategies for many of the different subtypes remain unknown. Here, we identify that bithalamic gliomas harbor frequent mutations in the EGFR oncogene, only rare histone H3 mutation (in contrast to their unilateral counterparts), and a distinct genome-wide DNA methylation profile compared to all other glioma subtypes studied to date. These EGFR mutations are either small in-frame insertions within exon 20 (intracellular tyrosine kinase domain) or missense mutations within exon 7 (extracellular ligand-binding domain) that occur in the absence of accompanying gene amplification. We find these EGFR mutations are oncogenic in primary astrocyte models and confer sensitivity to specific tyrosine kinase inhibitors dependent on location within the kinase domain or extracellular domain. We initiated treatment with targeted kinase inhibitors in four children whose tumors harbor EGFR mutations with encouraging results. This study identifies a promising genomically-tailored therapeutic strategy for bithalamic gliomas, a lethal and genetically distinct brain tumor of childhood.

Journal Title: Acta neuropathologica

PUBMED ID: 32285998

DOI: doi.org/10.1002/pbc.28283

Titolo: A phase 2 study of valproic acid and radiation, followed by maintenance valproic acid and bevacizumab in children with newly diagnosed diffuse intrinsic pontine glioma or high-grade glioma.

Autori: Su JM., Murray JC., McNall-Knapp RY., Bowers DC., Shah S., Adesina A M., Paulino AC., Jo E., Mo Q., Baxter PA., Blaney SM.

Data di Pubblicazione: 2020-4-15

Abstract: Addition of VPA and bevacizumab to radiation was well tolerated but did not appear to improve EFS or OS in children with DIPG or HGG.

Journal Title: Pediatric blood & cancer

PUBMED ID: 32249134

DOI: doi.org/10.1016/j.jmir.2020.01.007

Titolo: Cannabis and Radiation Therapy: A Scoping Review of Human Clinical Trials.

Autori: Rosewall T., Feuz C., Bayley A.

Data di Pubblicazione: 2020-4-7

Abstract: The existing body of literature evaluating the use of cannabinoids by patients undergoing RT is very limited. Well-designed randomized controlled trials are urgently needed, which address the significant design flaws of previous studies and evaluate the impact of phytocannabinoids in patients undergoing RT.

Journal Title: Journal of medical imaging and radiation sciences

PUBMED ID: 32245342

DOI: doi.org/10.1080/01616412.2020.1748323

Titolo: Low expression of

Autori: Zhu J., Zhao YP., Zhang YQ.

Data di Pubblicazione: 2020-4-5

Abstract: None

Journal Title: Neurological research

PUBMED ID: 32242226

DOI: doi.org/10.1093/neuonc/noaa077

Titolo: Clinical impact of combined epigenetic and molecular analysis of pediatric low grade gliomas.

Autori: Fukuoka K., Mamatjan Y., Tatevossian R., Zapotocky M., Ryall S., Stucklin AG., Bennett J., Nobre LF., Arnoldo A., Luu B., Wen J., Zhu K., Leon A., Torti D., Pugh TJ., Hazrati LN., Laperriere N., Drake J., Rutka JT., Dirks P., Kulkarni AV., Taylor MD., Bartels U., Huang A., Zadeh G., Aldape K., Ramaswamy V., Bouffet E., Snuderl M., Ellison D., Hawkins C., Tabori U.

Data di Pubblicazione: 2020-4-4

Abstract: The PLGG methylome is affected by multiple non-neoplastic factors. Combined molecular and pathological analysis is key to provide additional information when methylation classification is used for PLGG in the clinical setting.

Journal Title: Neuro-oncology

PUBMED ID: 32199197

DOI: doi.org/10.1016/j.ctrv.2020.101993

Titolo: Evolving role of regorafenib for the treatment of advanced cancers.

Autori: Grothey A., Blay JY., Pavlakis N., Yoshino T., Bruix J.

Data di Pubblicazione: 2020-3-22

Abstract: Regorafenib is an oral tyrosine kinase inhibitor (TKI) approved for the treatment of refractory metastatic colorectal cancer (mCRC), advanced gastrointestinal stromal tumors (GIST) previously treated with imatinib and sunitinib, and unresectable hepatocellular carcinoma (HCC) following progression on sorafenib. Regorafenib was initially approved for mCRC based on improved overall survival (OS) in the randomized, placebo-controlled, phase 3 CORECT trial, which was confirmed in an expanded population of Asian patients in the randomized, placebo-controlled phase 3 CONCUR trial. Approvals in GIST, and more recently in HCC, were based on the results from the randomized, placebo-controlled, phase 3 GRID and RESORCE trials, respectively. In this review, we provide a comprehensive summary of the clinical evidence for approval of regorafenib in mCRC, GIST, and HCC, present emerging evidence of regorafenib activity in other tumor types (namely, gastroesophageal cancer, sarcomas, biliary tract cancer, and glioblastoma), and discuss trials in progress within the context of regorafenib's mechanism of action. We describe recent advances and key lessons learned with regorafenib, including the importance of managing common drug-related toxicities using dose-optimization strategies, the search for biomarkers to predict response to treatment, and highlight some of the unaddressed questions and future directions for regorafenib across tumors.

Journal Title: Cancer treatment reviews

PUBMED ID: 32197147

DOI: doi.org/10.1016/j.tranon.2020.100755

Titolo: Cancer Stem Cell Chemotherapeutics Assay for Prospective Treatment of Recurrent Glioblastoma and Progressive Anaplastic Glioma: A Single-Institution Case Series.

Autori: Ranjan T., Howard CM., Yu A., Xu L., Aziz K., Jho D., Leonardo J., Hameed MA., Karlovits SM., Wegner RE., Fuhrer R., Lirette ST., Denning KL., Valluri J., Claudio PP.

Data di Pubblicazione: 2020-3-21

Abstract: Glioblastoma (GBM) and progressive anaplastic glioma are the most aggressive brain tumor in adults and their prognosis is very poor even if treated with the standard of care chemoradiation Stupp's protocol. Recent knowledge pointed out that current treatments often fail to successfully target cancer stem cells (CSCs) that are responsible for therapy resistance and recurrence of these malignant tumors. ChemoID is the first and only CLIA (clinical laboratory improvements amendment) -certified and CAP (College of American

an Pathologists) -accredited chemotherapeutic assay currently available in oncology clinics that examines patient's derived CSCs susceptibility to conventional FDA (Food and Drugs Administration) -approved drugs. In this study we observed that although the majority of our patients (71.5%) presented with unfavorable prognostic predictors (wild type IDH-1/2 and unmethylated MGMT promoter), patients treated with ChemoID assay-directed therapy had an overall response rate of 86% and increased median OS of 13.3 months compared to the historical median OS of 9.1 months (8.1-10.1 months) previously reported [1] suggesting that the ChemoID assay may be beneficial in personalizing treatment strategies.

Journal Title: Translational oncology

PUBMED ID: 32191542

DOI: doi.org/10.1200/CCI.19.00121

Titolo: Cancer Imaging Phenomics via CaPTk: Multi-Institutional Prediction of Progression-Free Survival and Pattern of Recurrence in Glioblastoma.

Autori: Fathi Kazerooni A., Akbari H., Shukla G., Badve C., Rudie JD., Sako C., Rathore S., Bakas S., Pati S., Singh A., Bergman M., Ha SM., Kontos D., Nasrallah M., Bagley SJ., Lustig RA., O'Rourke DM., Sloan AE., Barnholtz-Sloan JS., Mohan S., Bilello M., Davatzikos C.

Data di Pubblicazione: 2020-3-20

Abstract: Imaging signatures of presurgical MP-MRI scans reveal relatively high predictability of time and location of GBM recurrence, subject to the patients receiving standard first-line chemoradiation therapy. Through its graphical user interface, CaPTk offers easy accessibility to advanced computational algorithms for deriving imaging signatures predictive of clinical outcome and could similarly be used for a variety of radiomic and radiogenomic analyses.

Journal Title: JCO clinical cancer informatics

PUBMED ID: 32154775

DOI: doi.org/10.1148/radiol.2020191376

Titolo: Identification of Early Response to Anti-Angiogenic Therapy in Recurrent Glioblastoma: Amide Proton Transfer-weighted and Perfusion-weighted MRI compared with Diffusion-weighted MRI.

Autori: Park JE., Kim HS., Park SY., Jung SC., Kim JH., Heo HY.

Data di Pubblicazione: 2020-3-11

Abstract: Background Amide proton transfer (APT) MRI has the potential to demonstrate antitumor effects by reflecting biologically active tumor portion, providing different information from diffusion-weighted imaging (DWI) or dynamic susceptibility contrast (DSC) imaging. Purpose To evaluate whether a change in APT signal intensity after antiangiogenic treatment is predictive of early treatment response in recurrent glioblastoma. Materials and Methods In this retrospective study, APT MRI, DWI, and DSC imaging were performed in patients with recurrent glioblastoma from July 2015 to April 2019, both before treatment and 4-6 weeks after initiation of bevacizumab (follow-up). Progression was based on pathologic confirmation or clinical-radiologic assessment, and progression patterns were defined as local enhancing or diffuse nonenhancing. Changes in mean and histogram parameters (fifth and 95th percentiles) of APT signal intensity, apparent diffusion coefficient, and normalized cerebral blood volume (CBV) between imaging time points were calculated. Predictors of 12-month progression and progression-free survival (PFS) were determined by using logistic regression and Cox proportional hazard modeling and according to progression type. Results A total of 54 patients were included (median age, 56 years [interquartile range, 49-64 years]; 24 men). Mean APT signal intensity change after bevacizumab treatment indicated a low 12-month progression rate (odds ratio [OR], 0.36; 95% confidence interval [CI]: 0.13, 0.90;



Journal Title: Radiology

PUBMED ID: 32089384

DOI: doi.org/10.1016/j.jocn.2020.01.086

Titolo: Patterns of management and outcomes of unifocal versus multifocal glioblastoma.

Autori: Haque W., Thong Y., Verma V., Rostomily R., Brian Butler E., Teh BS.

Data di Pubblicazione: 2020-2-25

Abstract: This is the largest study to date describing outcomes for patients with multifocal GBM, and it shows that multifocal GBM is associated with a decreased use both of GTR and conventionally fractionated RT, as well as worse median OS. Further research is needed to improve clinical outcomes for patients with multifocal GBM.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 32074098

DOI: doi.org/10.3855/jidc.11582

Titolo: Nocardia farcinica meningitis in a patient with high-grade astrocytoma.

Autori: Nasri E., Fakhim H., Barac A., Yousefi S., Aghazade K., Boljevic D., Mardani M.

Data di Pubblicazione: 2020-2-20

Abstract: We describe a case of 91-year-old male with astrocytoma who developed meningitis caused by Nocardia farcinica. He had a past medical history of anaplastic astrocytoma grade III. Endocranial computed tomography (CT) scan revealed mass lesion in the left occipital region associated with perilesional edema, without evidence of midline shift issue. The analyses of cerebrospinal fluid (CSF) revealed neutrophilic pleocytosis, hyperproteinorrachia and hypoglycorrachia. Combined antimicrobial therapy was initiated (vancomycin, meropenem, acyclovir). CSF culture revealed Nocardia farcinica. Susceptibility testing revealed intermediate sensitivity to meropenem and antibiotic treatment was switched to trimethoprim-sulfamethoxazole and imipenem. After 7 days of treatment the patient developed progressive dyspnea. The chest CT scan revealed bilateral pleural effusion and alveolar infiltrate mostly in the right lobe. Ceftriaxone was added to the therapy, but the outcome was lethal. Nocardia spp. should be considered as differential diagnosis in the patients with brain tumor or meningitis in the setting of immune suppression and corticosteroid use. CSF cultures should be incubated longer with aim to allow fastidious organisms to grow, such as Nocardia spp.

Journal Title: Journal of infection in developing countries

PUBMED ID: 32055850

DOI: doi.org/10.1093/neuonc/noaa034

Titolo: Glycine by MR spectroscopy is an imaging biomarker of glioma aggressiveness.

Autori: Tiwari V., Daoud EV., Hatanpaa KJ., Gao A., Zhang S., An Z., Ganji S K., Raisanen JM., Lewis CM., Askari P., Baxter J., Levy M., Dimitrov I., Thomas BP., Pinho MC., Madden CJ., Pan E., Patel TR., DeBerardinis RJ., Sherry AD., Mickey BE., Malloy CR., Maher EA., Choi C.

Data di Pubblicazione: 2020-2-15

Abstract: 1. Glycine and 2-hydroxyglutarate in glioma patients are precisely co-detected using MRS at 3T.2. Tumors with elevated glycine proliferate and progress rapidly.3. A high glycine/2HG ratio is predictive of shortened patient survival.

Journal Title: Neuro-oncology

PUBMED ID: 32052049

DOI: doi.org/10.1093/neuonc/noaa031

Titolo: Risk stratification in pediatric low-grade glioma and glioneuronal tumor treated with radiation therapy: an integrated clinicopathologic and molecular analysis.

Autori: Acharya S., Liu JF., Tatevossian RG., Chiang J., Qaddoumi I., Gajjar A., Walker D., Harreld JH., Merchant TE., Ellison DW.

Data di Pubblicazione: 2020-2-14

Abstract: A high-risk subgroup of patients, defined by diffuse astrocytoma histology or midbrain/thalamus tumor location, have suboptimal long-term survival and might benefit from timely use of RT. These results require validation.

Journal Title: Neuro-oncology

PUBMED ID: 32034261

DOI: doi.org/10.1038/s41598-020-59152-7

Titolo: The application of point source electroporation and chemotherapy for the treatment of glioma: a randomized controlled rat study.

Autori: Sharabi S., Guez D., Daniels D., Cooper I., Atrakchi D., Liraz-Zaltsman S., Last D., Mardor Y.

Data di Pubblicazione: 2020-2-9

Abstract: The prognosis of Glioblastoma Multiforme patients is poor despite aggressive therapy. Reasons include poor chemotherapy penetration across the blood-brain barrier and tumor infiltration into surrounding tissues. Here we studied the effects of combined point-source electroporation (EP) and systemic chemotherapy in glioma-bearing rats. 128 rats were studied. Treatment groups were administered systemic Cisplatin/Methotrexate before EP (either 90 or 180 pulses). Control groups were treated by EP, chemotherapy, or no treatment. Tumor volumes were determined by MRI. Tumors growth rates of the EP+Methotrexate group ( $1.02 \pm 0.77$ ) were significantly lower ( $p < 0.01$ ) than the control ( $5.2 \pm 1.0$ ) 1-week post treatment. No significant difference was found compared to Methotrexate ( $1.7 \pm 0.5$ ). Objective response rates (ORR) were 40% and 57% for the Methotrexate and EP+Methotrexate groups respectively. Tumor growth rates and ORR of the EP+Cisplatin groups (90 pulses  $0.98 \pm 0.2$ , 57%, 180 pulses  $1.2 \pm 0.1$ , 33%) were significantly smaller than the control ( $6.4 \pm 1.0$ ,  $p < 0.01$ ,  $p < 0.02$ , 0%) and Cisplatin ( $3.9 \pm 1.0$ ,  $p < 0.04$ ,  $p < 0.05$ , 13%) groups. No significant differences were found between the control groups. Increased survival was found in the EP+Cisplatin group, X

Journal Title: Scientific reports

PUBMED ID: 32034238

DOI: doi.org/10.1038/s41598-020-59089-x

Titolo: Extent of resection and molecular pathologic subtype are potent prognostic factors of adult WHO grade II glioma.

Autori: Choi J., Kim SH., Ahn SS., Choi HJ., Yoon HI., Cho JH., Roh TH., Kang SG., Chang JH., Suh CO.

Data di Pubblicazione: 2020-2-9

Abstract: We evaluated prognostic factors of adult low-grade glioma (LGG) according to the new 2016 WHO classification. Records of 153 patients diagnosed with WHO grade II LGG between 2003 and 2015 were retrospectively reviewed. Based on the 2016 WHO classification, 80 patients (52.3%) had diffuse astrocytoma, IDH-mutant; 45 (29.4%) had oligodendroglioma, IDH-mutant and 1p/19q-codeleted (ODG); and 28 (18.3%) had diffuse astrocytoma, IDH-wildtype. Gross total resection (GTR) was performed in 71 patients (46.4%), subtotal resection in 31 (20.3%), partial resection in 43 (28.1%), and biopsy in 8 (5.2%). One hundred two patients (66.7%) received postoperative radiotherapy. The 5-

and 10-year progression-free survival (PFS) rates were 72.7% and 51.5%, respectively, and the 5- and 10-year overall survival (OS) rates were 82.5% and 63.5%, respectively. GTR and IDH-mutant and/or 1p/19q codeletion were favorable prognostic factors for PFS and OS. Patients with IDH-wildtype had significantly decreased OS. Among patients with ODG who underwent GTR, no recurrence was observed after radiotherapy. Patients who underwent non-GTR frequently experienced recurrence after radiotherapy (IDH-mutant: 47.6%, IDH-wildtype: 57.9%). In conclusion, molecular classification of LGG was of prognostic relevance, with IDH-wildtype patients having a particularly poor outcome, regardless of the treatment. Favorable results were observed in patients who underwent GTR.

Journal Title: Scientific reports

PUBMED ID: 32034072

DOI: doi.org/10.1158/1078-0432.CCR-18-1140

Titolo: Rindopepimut with Bevacizumab for Patients with Relapsed EGFRvIII-Expressing Glioblastoma (ReACT): Results of a Double-Blind Randomized Phase II Trial.

Autori: Reardon DA., Desjardins A., Vredenburgh JJ., O'Rourke DM., Tran DD., Fink KL., Nabors LB., Li G., Bota DA., Lukas RV., Ashby LS., Duic JP., Mrugala MM., Cruickshank S., Vitale L., He Y., Green JA., Yellin MJ., Turner CD., Keler T., Davis TA., Sampson JH., Sampson JH.

Data di Pubblicazione: 2020-2-9

Abstract: Our randomized trial supports the potential for targeted immunotherapy among patients with GBM, but the therapeutic benefit requires validation due to the small sample size and potential heterogeneity of bevacizumab response among recurrent patients with GBM.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 32016716

DOI: doi.org/10.1007/s11060-020-03415-w

Titolo: Radiation dose response of neurologic symptoms during conformal radiotherapy for diffuse intrinsic pontine glioma.

Autori: Tinkle CL., Campbell K., Han Y., Li Y., Bianski B., Broniscer A., Khan RB., Merchant TE.

Data di Pubblicazione: 2020-2-5

Abstract: Low cumulative RT doses resulted in neurologic improvement in most patients with DIPG. The volume of brainstem spared by tumor influenced time to symptomatic improvement. Neurologic improvement during RT was associated with superior survival.

Journal Title: Journal of neuro-oncology

PUBMED ID: 31998633

DOI: doi.org/10.3389/fonc.2019.01436

Titolo: Personalized Treatment of H3K27M-Mutant Pediatric Diffuse Gliomas Provides Improved Therapeutic Opportunities.

Autori: Gojo J., Pavelka Z., Zapletalova D., Schmook MT., Mayr L., Madlener S., Kyr M., Vejmelkova K., Smrcka M., Czech T., Dorfer C., Skotakova J., Azizi AA., Chocholous M., Reisinger D., Lastovicka D., Valik D., Haberler C., Pfeyrl A., Noskova H., Pál K., Jezova M., Veselska R., Kozakova S., Slaby O., Slavc I., Sterba J.

Data di Pubblicazione: 2020-1-31

Abstract: Diffuse gliomas with K27M histone mutations (H3K27M glioma) are generally characterized by a fatal prognosis, particularly affecting the pediatric population. Based on the molecular heterogeneity observed in this tumor type, personalized treatment is considered to substantially improve therapeutic

tic options. Therefore, clinical evidence for therapy, guided by comprehensive molecular profiling, is urgently required. In this study, we analyzed feasibility and clinical outcomes in a cohort of 12 H3K27M glioma cases treated at two centers. Patients were subjected to personalized treatment either at primary diagnosis or disease progression and received backbone therapy including focal irradiation. Molecular analyses included whole-exome sequencing of tumor and germline DNA, RNA-sequencing, and transcriptomic profiling. Patients were monitored with regular clinical as well as radiological follow-up. In one case, liquid biopsy of cerebrospinal fluid (CSF) was used. Analyses could be completed in 83% (10/12) and subsequent personalized treatment for one or more additional pharmacological therapies could be recommended in 90% (9/10). Personalized treatment included inhibition of the PI3K/AKT/mTOR pathway (3/9), MAPK signaling (2/9), immunotherapy (2/9), receptor tyrosine kinase inhibition (2/9), and retinoic receptor agonist (1/9). The overall response rate within the cohort was 78% (7/9) including one complete remission, three partial responses, and three stable diseases. Sustained responses lasting for 28 to 150 weeks were observed for cases with

Journal Title: Frontiers in oncology

PUBMED ID: 31973881

DOI: doi.org/10.1016/j.tips.2019.12.003

Titolo: Immunotherapy for Malignant Glioma: Current Status and Future Directions.

Autori: Wang H., Xu T., Huang Q., Jin W., Chen J.

Data di Pubblicazione: 2020-1-25

Abstract: Glioma is the most common intracranial primary malignancy, with limited treatment options and a poor overall survival (OS). Immunotherapy has been used successfully in various cancers, leading to the development of similar therapies that activate the patient's immune system to eliminate glioma. In this review, we introduce the diverse immunotherapeutic approaches available for treating glioma, highlighting the successes and challenges resulting from current clinical trials. Additionally, we emphasize the effect of multiple clinical factors on immunotherapy to help optimize individualized treatment regimens. Finally, we also highlight several novel concepts and technologies that could be used to design new and/or improve existing immunotherapies. Such approaches will delineate a new blueprint for glioma treatment.

Journal Title: Trends in pharmacological sciences

PUBMED ID: 31971950

DOI: doi.org/10.1371/journal.pone.0227693

Titolo: Treatment of children under 4 years of age with medulloblastoma and ependymoma in the HIT2000/HIT-REZ 2005 trials: Neuropsychological outcome 5 years after treatment.

Autori: Ottensmeier H., Schlegel PG., Eyrich M., Wolff JE., Juhnke BO., von Hoff K., Frahssek S., Schmidt R., Faldum A., Fleischhack G., von Bueren A., Friedrich C., Resch A., Warmuth-Metz M., Krauss J., Kortmann RD., Bode U., Kühl J., Rutkowski S.

Data di Pubblicazione: 2020-1-24

Abstract: Young children with brain tumours are at high risk of developing treatment-related sequelae. We aimed to assess neuropsychological outcomes 5 years after treatment. This cross-sectional study included children under 4 years of age with medulloblastoma (MB) or ependymoma (EP) enrolled in the German brain tumour trials HIT2000 and HIT-REZ2005. Testing was performed using the validated Wuerzburg Intelligence Diagnostics (WUEP-D), which includes Kaufman-Assessment-Battery, Coloured Progressive Matrices, Visual-Motor Integration, finger tapping "Speed", and the Continuous Performance Test. Of 104 patients in 47 centres, 72 were eligible for analyses. We assessed whether IQ was impacted by disease extent, disease location, patient age, gender, age

at surgery, and treatment (chemotherapy with or without craniospinal irradiation [CSI] or local radiotherapy [LRT]). Median age at surgery was 2.3 years. Testing was performed at a median of 4.9 years after surgery. Patients with infratentorial EPs (treated with LRT) scored highest in fluid intelligence (CPM  $100.9 \pm 16.9$ , mean  $\pm$  SD); second best scores were achieved by patients with MB without metastasis treated with chemotherapy alone (CPM  $93.9 \pm 13.2$ ), followed by patients with supratentorial EPs treated with LRT. In contrast, lowest scores were achieved by patients that received chemotherapy and CSI, which included children with metastasised MB and those with relapsed MB M0 (CPM  $71.7 \pm 8.0$  and  $73.2 \pm 21.8$ , respectively). Fine motor skills were reduced in all groups. Multivariable analysis revealed that type of treatment had an impact on IQ, but essentially not age at surgery, time since surgery or gender. Our results confirm previous reports on the detrimental effects of CSI in a larger cohort of children. Comparable IQ scores in children with MB treated only with chemotherapy and in children with EP suggest that this treatment strategy represents an attractive option for children who have a high chance to avoid application of CSI. Longitudinal follow-up examinations are warranted to assess long-term neuropsychological outcomes.

Journal Title: PloS one

PUBMED ID: 31936544

DOI: doi.org/10.3390/ijms21020423

Titolo: Crocetin Extracted from Saffron Shows Antitumor Effects in Models of Human Glioblastoma.

Autori: Colapietro A., Mancini A., Vitale F., Martellucci S., Angelucci A., Llorens S., Mattei V., Gravina GL., Alonso GL., Festuccia C.

Data di Pubblicazione: 2020-1-16

Abstract: Over recent years, many authors discussed the effects of different natural compounds on glioblastoma (GBM). Due to its capacity to impair survival and progression of different cancer types, saffron extract (SE), named crocetin (CCT), is particularly noteworthy. In this work, we elucidated the antitumor properties of crocetin in glioma in vivo and in vitro models for the first time. The in vitro results showed that the four tumor cell lines observed in this study (U251, U87, U138, and U373), which were treated with increasing doses of crocetin, showed antiproliferative and pro-differentiative effects as demonstrated by a significant reduction in the number of viable cells, deep changes in cell morphology, and the modulation of mesenchymal and neuronal markers. Indeed, crocetin decreased the expression of Cluster of Differentiation CD44, CD90, CXCR4, and OCT3/4 mesenchymal markers, but increased the expression of  $\beta$ Tubulin and neurofilaments (NFH) neuronal lineage-related markers. Epigenetic mechanisms may modulate these changes, since Histone Deacetylase, HDAC1 and HDAC3 were downmodulated in U251 and U87 cells, whereas HDAC1 expression was downmodulated in U138 and U373 cells. Western blotting analyses of Fatty Acid Synthase, FASN, and CD44 resulted in effective inhibition of these markers after CCT treatment, which was associated with important activation of the apoptosis program and reduced glioma cell movement and wound repair. The in vivo studies aligned with the results obtained in vitro. Indeed, crocetin was demonstrated to inhibit the growth of U251 and U87 cells that were subcutaneously injected into animal models. In particular, the Tumor To Progression or TTP values and Kaplan-Meier curves indicated that crocetin had more major effects than radiotherapy alone, but similar effects to temozolomide (TMZ). An intra-brain cell inoculation of a small number of luciferase-transfected U251 cells provided a model that was able to recapitulate recurrence after surgical tumor removal. The results obtained from the orthotopic intra-brain model indicated that CCT treatment increased the disease-free survival (DFS) and overall survival (OS) rates, inducing a delay in appearance of a detectable bioluminescent lesion. CCT showed greater efficacy than Radio Therapy (RT) but comparable efficacy to temozolomide in xenograft models. Therefore, we aimed to continue the study of crocetin's effects

cts in glioma disease, focusing our attention on the radiosensitizing properties of the natural compound and highlighting the ways in which this was realized.

Journal Title: International journal of molecular sciences

PUBMED ID: 31914946

DOI: doi.org/10.1186/s12885-019-6467-6

Titolo: Combining therapy with recombinant human endostatin and cytotoxic agents for recurrent disseminated glioblastoma: a retrospective study.

Autori: Ge JJ., Li C., Qi SP., Xue FJ., Gao ZM., Yu CJ., Zhang JP.

Data di Pubblicazione: 2020-1-10

Abstract: Rh-ES, in combination with cytotoxic drugs, was an alternative effective regimen with manageable toxicities in treatment of recurrent disseminated glioblastoma.

Journal Title: BMC cancer

PUBMED ID: 31908598

DOI: doi.org/10.1186/s12935-019-1086-5

Titolo: Patient-derived xenografts of different grade gliomas retain the heterogeneous histological and genetic features of human gliomas.

Autori: Zeng W., Tang Z., Li Y., Yin G., Liu Z., Gao J., Chen Y., Chen F.

Data di Pubblicazione: 2020-1-8

Abstract: The panel of patient-derived glioma xenografts in this study reproduced the diverse heterogeneity of different grade gliomas, thereby allowing the study of the growth characteristics of various glioma types and the identification of tumor-specific molecular markers, which has applications in drug discovery and patient-tailored therapy.

Journal Title: Cancer cell international

PUBMED ID: 31896084

DOI: doi.org/10.3171/2019.10.FOCUS19726

Titolo: Blood-brain barrier disruption with low-intensity pulsed ultrasound for the treatment of pediatric brain tumors: a review and perspectives.

Autori: Beccaria K., Canney M., Bouchoux G., Puget S., Grill J., Carpentier A.

Data di Pubblicazione: 2020-1-3

Abstract: Pediatric brain tumors are the most common solid tumor and the first cause of cancer death in childhood, adolescence, and young adulthood. Current treatments are far from optimal in most of these tumors and the prognosis remains dismal for many of them. One of the main causes of the failure of current medical treatments is in part due to the existence of the blood-brain barrier (BBB), which limits drug delivery to tumors. Opening of the BBB with low-intensity pulsed ultrasound (LIPU) has emerged during the last 2 decades as a promising technique for enhancing drug delivery to the brain. In preclinical models, enhanced delivery of a wide range of therapeutic agents, from low-molecular-weight drugs, to antibodies and immune cells, has been observed as well as tumor control and increased survival. This technique has recently entered clinical trials with extracranial and intracranial devices. The safety and feasibility of this technique has furthermore been shown in patients treated monthly for recurrent glioblastoma receiving carboplatin chemotherapy. In this review, the characteristics of the BBB in the most common pediatric brain tumors are reviewed. Then, principles and mechanisms of BBB disruption with ultrasound (US) are summarized and described at the histological and biological levels. Lastly, preclinical studies that have used US-induced BBB opening in tumor models, recent clinical trials, and the potential use of this technology in pediatrics are provided.

Journal Title: Neurosurgical focus

PUBMED ID: 31842801  
DOI: doi.org/10.1186/s12885-019-6414-6  
Titolo: A systematic analysis of immune genes and overall survival in cancer patients.  
Autori: Wang Q., Li P., Wu W.  
Data di Pubblicazione: 2019-12-18  
Abstract: The TCR signaling pathway played a distinct role in the OS of these 6 cancer types.  
Journal Title: BMC cancer

PUBMED ID: 31819537  
DOI: doi.org/10.2147/OTT.S226804  
Titolo: Apatinib Plus Temozolomide for Recurrent Glioblastoma: An Uncontrolled, Open-Label Study.  
Autori: Wang Y., Meng X., Zhou S., Zhu Y., Xu J., Tao R.  
Data di Pubblicazione: 2019-12-11  
Abstract: Apatinib combined with dose-dense TMZ was effective in terms of PFS, ORR, and DCR and was well tolerated after appropriate dose reduction in the Chinese population tested. Further randomized controlled clinical studies are needed to confirm the efficacy of apatinib combined with TMZ for treatment of rGBM.  
Journal Title: OncoTargets and therapy

PUBMED ID: 31785339  
DOI: doi.org/10.1016/j.ijrobp.2019.11.020  
Titolo: Defining Optimal Target Volumes of Conformal Radiation Therapy for Diffuse Intrinsic Pontine Glioma.  
Autori: Tinkle CL., Simone B., Chiang J., Li X., Campbell K., Han Y., Li Y., Hover LD., Molitoris JK., Becksfort J., Lucas JT., Patay Z., Baker SJ., Broniscer A., Merchant TE.  
Data di Pubblicazione: 2019-12-1  
Abstract: All patients who experienced local failure showed progression within the high-dose volume, and there was no apparent survival or tumor-control benefit to extending the CTV margins beyond 1 cm. Given the increasing use of reirradiation, standardizing the CTV margin to 1 cm may improve retreatment tolerance.  
Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 31785177  
DOI: doi.org/10.1111/ped.14070  
Titolo: Hypofractionated radiotherapy in children with diffuse intrinsic pontine glioma.  
Autori: Hayashi A., Ito E., Omura M., Aida N., Tanaka M., Tanaka Y., Sato H., Miyagawa N., Yokosuka T., Iwasaki F., Hamanoue S., Goto H.  
Data di Pubblicazione: 2019-12-1  
Abstract: Hypofractionated RT for children with newly diagnosed DIPG is well tolerated and feasible from the viewpoint of reducing a patient's burden of treatment. Re-irradiation at first progression is suggested to be beneficial.  
Journal Title: Pediatrics international : official journal of the Japan Pediatric Society

PUBMED ID: 31782181  
DOI: doi.org/10.1002/ana.25655

Titolo: Randomized Placebo-Controlled Trial of Intravenous Immunoglobulin in Autoimmune LGI1/CASPR2 Epilepsy.

Autori: Dubey D., Britton J., McKeon A., Gadoth A., Zekeridou A., Lopez Chiriboga SA., Devine M., Cerhan JH., Dunlay K., Sagen J., Ramberger M., Waters P., Irani SR., Pittock SJ.

Data di Pubblicazione: 2019-11-30

Abstract: Superiority of IVIG to placebo reached statistical significance for the primary endpoint for all patients and the subset with LGI1-IgG. These results have to be interpreted with the caveat that the study did not reach its originally selected sample size. ANN NEUROL 2020;87:313-323.

Journal Title: Annals of neurology

PUBMED ID: 31779130

DOI: doi.org/10.3390/ijms20235942

Titolo: CSPG4 as Target for CAR-T-Cell Therapy of Various Tumor Entities-Merits and Challenges.

Autori: Harrer DC., Dörrie J., Schaft N.

Data di Pubblicazione: 2019-11-30

Abstract: Targeting cancer cells using chimeric-antigen-receptor (CAR-)T cells has propelled adoptive T-cell therapy (ATT) to the next level. A plentitude of durable complete responses using CD19-specific CAR-T cells in patients suffering from various lymphoid malignancies resulted in the approval by the food and drug administration (FDA) of CD19-directed CAR-T cells for the treatment of acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL). A substantial portion of this success in hematological malignancies can be traced back to the beneficial properties of the target antigen CD19, which combines a universal presence on target cells with no detectable expression on indispensable host cells. Hence, to replicate response rates achieved in ALL and DLBCL in the realm of solid tumors, where ideal target antigens are scant and CAR-T cells are still lagging behind expectations, the quest for appropriate target antigens represents a crucial task to expedite the next steps in the evolution of CAR-T-cell therapy. In this review, we want to highlight the potential of chondroitin sulfate proteoglycan 4 (CSPG4) as a CAR-target antigen for a variety of different cancer entities. In particular, we discuss merits and challenges associated with CSPG4-CAR-T cells for the ATT of melanoma, leukemia, glioblastoma, and triple-negative breast cancer.

Journal Title: International journal of molecular sciences

PUBMED ID: 31766326

DOI: doi.org/10.3390/jcm8122031

Titolo: Regorafenib CSF Penetration, Efficacy, and MRI Patterns in Recurrent Malignant Glioma Patients.

Autori: Zeiner PS., Kinzig M., Divé I., Maurer GD., Filipinski K., Harter PN., Senft C., Bähr O., Hattingen E., Steinbach JP., Sörgel F., Voss M., Steidl E., Ronellenfitsch MW.

Data di Pubblicazione: 2019-11-27

Abstract: (1) Background: The phase 2 Regorafenib in Relapsed Glioblastoma (REGOMA) trial indicated a survival benefit for patients with first recurrence of a glioblastoma when treated with the multikinase inhibitor regorafenib (REG) instead of lomustine. The aim of this retrospective study was to investigate REG penetration to cerebrospinal fluid (CSF), treatment efficacy, and effects on magnetic resonance imaging (MRI) in patients with recurrent high-grade gliomas. (2) Methods: Patients were characterized by histology, adverse events, steroid treatment, overall survival (OS), and MRI growth pattern. REG and its two active metabolites were quantified by liquid chromatography/tandem mass spectrometry in patients' serum and CSF. (3) Results: 21 patients mainly with IDH-wildtype glioblastomas who had been treated with REG were



retrospectively identified. Thirteen CFS samples collected from 3 patients of the cohort were available for pharmacokinetic testing. CSF levels of REG and its metabolites were significantly lower than in serum. Follow-up MRI was available in 19 patients and showed progressive disease (PD) in all but 2 patients. Two distinct MRI patterns were identified: 7 patients showed classic PD with progression of contrast enhancing lesions, whereas 11 patients showed a T2-dominant MRI pattern characterized by a marked reduction of contrast enhancement. Median OS was significantly better in patients with a T2-dominant growth pattern (10 vs. 27 weeks respectively,  
Journal Title: Journal of clinical medicine

PUBMED ID: 31760930

DOI: doi.org/10.2174/1389557519666191018155426

Titolo: Will Arsenic Trioxide Benefit Treatment of Solid Tumor by Nano- Encapsulation?

Autori: Fu X., Li YS., Zhao J., Yu LL., Luo RG., Liang QR., Tang Q.

Data di Pubblicazione: 2019-11-26

Abstract: Arsenic trioxide (ATO) has remarkably enhanced therapeutic efficacy in treating both newly diagnosed and relapsed patients suffering from Acute Promyelocytic Leukemia (APL). Unfortunately, whether as a single agent, component of combined chemotherapy, or as a chemosensitizer or radiosensitizer combined with interventional therapy/radiotherapy, it did not benefit treatment of solid tumor (liver cancer, bladder cancer, glioma, breast cancer, cervical cancer, colorectal cancer, lung cancer, and melanoma) as seen from the clinical trials reported from the published journals or FDA-approved trials in the past decades. The clinical outcome failed to live up to our expectations, which was attributed to severe systemic toxicity and inappropriate pharmacokinetic such as low delivery efficiency and rapid renal elimination. Nanomedicine is designed to fuel up pharmaceuticals and polish off adverse effects by the moderation of their absorption, distribution, metabolism, and excretion. Nevertheless, quite a few nanodrugs (such as Doxil, Abraxane) were approved to be used clinically, and "from bench to bedside" it seems to be no easy way for most of them, such as nano-ATO. Encapsulating ATO into several types of nano-vehicles (liposome, polymer micelle, porous silicon, etc.), nano-ATO can improve pharmacokinetic and become a prominent candidate to penetrate into tumor tissue, but so far no nano-ATO clinical trials have been approved around the world. On summarizing the clinical trials of ATO on solid tumor and preclinical study of nano-ATO, it is believed there is still a chance for ATO to play a critical co-helper in a comprehensive therapy to fight with solid tumor.

Journal Title: Mini reviews in medicinal chemistry

PUBMED ID: 31756059

DOI: doi.org/10.1002/cam4.2616

Titolo: Similar overall survival with reduced vs. standard dose bevacizumab monotherapy in progressive glioblastoma.

Autori: Gleeson JP., Keane F., Keegan NM., Mammadov E., Harrold E., Alhusaini A., Harte J., Eakin-Love A., O'Halloran PJ., MacNally S., Hennessy BT., Brathnach OS., Grogan L., Morris PG.

Data di Pubblicazione: 2019-11-23

Abstract: In this retrospective study, reduced-dose bevacizumab schedule resulted in similar OS to standard-dose bevacizumab monotherapy with substantial cost savings. MGMT methylation appears to convey a survival benefit in the setting of bevacizumab treatment for progressive GBM.

Journal Title: Cancer medicine

PUBMED ID: 31755915

DOI: doi.org/10.1093/neuonc/noz185

Titolo: Window-of-opportunity clinical trial of pembrolizumab in patients with recurrent glioblastoma reveals predominance of immune-suppressive macrophages.

Autori: de Groot J., Penas-Prado M., Alfaro-Munoz K., Hunter K., Pei BL., O'Brien B., Weathers SP., Loghin M., Kamiya Matsouka C., Yung WKA., Mandel J., Wu J., Yuan Y., Zhou S., Fuller GN., Huse J., Rao G., Weinberg JS., Prabhu S S., McCutcheon IE., Lang FF., Ferguson SD., Sawaya R., Colen R., Yadav SS., Blando J., Vence L., Allison J., Sharma P., Heimberger AB.

Data di Pubblicazione: 2019-11-23

Abstract: Immune analyses indicated that pembrolizumab anti-programmed cell death 1 (PD-1) monotherapy alone can't induce effector immunologic response in most GBM patients, probably owing to a scarcity of T cells within the tumor microenvironment and a CD68+ macrophage preponderance.

Journal Title: Neuro-oncology

PUBMED ID: 31741234

DOI: doi.org/10.1007/s11060-019-03344-3

Titolo: A multi-institutional analysis of clinical outcomes and patterns of care of 1p/19q codeleted oligodendrogliomas treated with adjuvant or salvage radiation therapy.

Autori: Lin AJ., Kane LT., Molitoris JK., Smith DR., Dahiya S., Badiyan SN., Wang TJC., Kruser TJ., Huang J.

Data di Pubblicazione: 2019-11-20

Abstract: Delaying RT for selected oligodendroglioma patients appears safe. Adjuvant chemotherapy does not delay SRT longer than observation and may be associated with worse PFS after RT.

Journal Title: Journal of neuro-oncology

PUBMED ID: 31728883

DOI: doi.org/10.1007/s11060-019-03340-7

Titolo: Hypofractionated radiotherapy with temozolomide in diffuse intrinsic pontine gliomas: a randomized controlled trial.

Autori: Izzuddeen Y., Gupta S., Haresh KP., Sharma D., Giridhar P., Rath GK.

Data di Pubblicazione: 2019-11-16

Abstract: The above study shows that hypofractionated radiotherapy with concurrent and adjuvant temozolomide does not improve OS and has higher hematological toxicity. Conventional radiotherapy remains the standard of care.

Journal Title: Journal of neuro-oncology

PUBMED ID: 31728705

DOI: doi.org/10.1007/s00381-019-04420-9

Titolo: Proton therapy for newly diagnosed pediatric diffuse intrinsic pontine glioma.

Autori: Muroi A., Mizumoto M., Ishikawa E., Ihara S., Fukushima H., Tsurubuchi T., Sakurai H., Matsumura A.

Data di Pubblicazione: 2019-11-16

Abstract: Proton therapy was well tolerated by the majority of patients. No severe adverse events, including radiation necrosis, were recorded. Proton therapy did not yield superior survival outcomes vs. conventional photon radiotherapy in patients with DIPG at our institution. Further research is needed to identify the factors associated with better survival in this population.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 31672491

DOI: doi.org/10.1016/j.canlet.2019.10.034

Titolo: Imatinib revives the therapeutic potential of metformin on ewing sarcoma by attenuating tumor hypoxic response and inhibiting convergent signaling pathways.

Autori: Nan X., Wang J., Cheng H., Yin Z., Sheng J., Qiu B., Lau CC., Yustein JT., Zhao H., Wong STC.

Data di Pubblicazione: 2019-11-2

Abstract: Ewing sarcoma (EwS) is an aggressive pediatric tumor treated with intensive cytotoxic chemotherapies. Overall survival for metastatic or relapsed disease is only 20-30%. Metformin has long been an attractive therapeutic option for EwS, but hypoxia limits its efficacy. Through a systematic integration of drug combination screening, bioinformatics analyses, functional and in vivo studies, and correlation with clinical outcome, we identified another known drug, imatinib that could augment the in vivo anti-tumor capacity of metformin by attenuating tumor hypoxic response. This drug combination regimen widely suppressed multiple dominant mechanisms in EwS genesis, growth, and metastasis, including key EWS-FLI1 downstream targets that converge into the PI3K/AKT/mTOR signaling pathway. In addition, the combination significantly enhanced inhibition on tumor cell proliferation by standard EwS chemotherapy drugs, including cyclophosphamide and ifosfamide. This suggests a potential clinical benefit of the metformin/imatinib combination by allowing the reduction in dose intensity of standard chemotherapy without compromising survival outcome and represents a potential faster track application for EwS patients.

Journal Title: Cancer letters

PUBMED ID: 31643011

DOI: doi.org/10.1007/s11060-019-03304-x

Titolo: Treatment strategies for glioblastoma in older patients: age is just a number.

Autori: Youssef M., Ludmir EB., Mandel JJ., Patel AJ., Jalali A., Treiber J., Wu J., McAleer MF., de Groot JF.

Data di Pubblicazione: 2019-10-24

Abstract: Our cohort of elderly GBM patients was predominantly treated with standard of care therapy based on EORTC 22,981. Despite their age, these patients generally tolerated treatment well and had favorable outcomes compared to those reported for patients treated on EORTC 22,981. Based on these findings, using advanced age as the basis for treatment de-escalation or as an exclusionary criterion in clinical trials should be discouraged.

Journal Title: Journal of neuro-oncology

PUBMED ID: 31625205

DOI: doi.org/10.1111/neup.12594

Titolo: Analysis of PD-L1 expression and T cell infiltration in different molecular subgroups of diffuse midline gliomas.

Autori: Jha P., Manjunath N., Singh J., Mani K., Garg A., Kaur K., Sharma MC., Raheja A., Suri A., Sarkar C., Suri V.

Data di Pubblicazione: 2019-10-19

Abstract: Diffuse midline gliomas (DMGs) are rare and devastating tumors with limited therapeutic options. Programmed death-ligand 1 (PD-L1) expression represents a potential predictive biomarker for immunotherapy. One hundred and twenty-six DMGs (89 adult and 37 pediatric) were assessed for immune profile (PD-L1, cluster of differentiation (CD3, CD8) and genetic markers (mutation in 27th amino acid of histone H3 (H3K27M), alpha thalassemia/mental retardation syndrome X-linked (ATRX), isocitrate dehydrogenase 1 (IDH1), p53) by immunohistochemistry. Sanger sequencing was done for IDH1 and H3K27M. The thalamus was the commonest site. Four molecular subgroups of DMGs were identified.

ied. H3K27M mutation was more frequent in children ( $P = 0.0001$ ). The difference in median overall survival (OS) was not significant in any of the four molecular subgroups ( $P > 0.05$ ). PD-L1 expression was significantly higher in H3K27M/IDH1 double-negative adult glioblastomas (GBMs) ( $P = 0.002$ ). Strong PD-L1 expression was more frequent in grade IV tumors and thalamic location, although the difference was not significant ( $P = 0.14$  and  $P = 0.19$  respectively). Positive PD-L1 expression was significantly associated with high tumor-infiltrating lymphocytes count ( $P < 0.05$ ). There was no significant difference in median OS in PD-L1-positive versus negative cases among four genetic subgroups ( $P > 0.05$ ). On univariate analysis, there was no direct correlation of PD-L1 with any genetic alteration, except H3K27M mutation ( $P = 0.01$ ). CD3 infiltration was similar in both adults and pediatric ages (84.3% and 78.4%, respectively) while CD8 expression was significantly greater in adults compared to children (74.1% vs 37.8%,  $P = 0.0001$ ). This is the first comprehensive analysis highlighting molecular and immune profiles of DMGs. Despite molecular and clinicopathological diversity, overall survival in DMGs remains dismal. Multicentric studies with larger numbers of cases should be undertaken for stratifying DMGs according to their age, immune and molecular profiles, to develop effective immunotherapies.

Journal Title: Neuropathology : official journal of the Japanese Society of Neuropathology

PUBMED ID: 31624332

DOI: doi.org/10.1038/s41397-019-0107-z

Titolo: ABCB1 single-nucleotide variants and survival in patients with glioblastoma treated with radiotherapy concomitant with temozolomide.

Autori: Malmström A., Łysiak M., Åkesson L., Jakobsen I., Mudaisi M., Milos P., Hallbeck M., Fomichov V., Broholm H., Grunnet K., Poulsen HS., Bratthall C., Strandeus M., Papagiannopoulou A., Stenmark-Askmal M., Green H., Söderkvist P.

Data di Pubblicazione: 2019-10-19

Abstract: Standard treatment for glioblastoma (GBM) patients is surgery and radiochemotherapy (RCT) with temozolomide (TMZ). TMZ is a substrate for ABCB1, a transmembrane drug transporter. It has been suggested that survival for GBM patients receiving TMZ is influenced by different single-nucleotide variants (SNV) of ABCB1. We therefore examined SNV:s of ABCB1, namely 1199G>A, 1236C>T, 2677G>T/A, and 3435C>T and correlated to survival for GBM patients receiving RCT. In a pilot cohort (97 patients) a significant correlation to survival was found for SNV 1199G>A, with median OS for variant G/G patients being 18.2 months versus 11.5 months for A/G ( $p=0.012$ ). We found no correlation to survival for the other SNV:s. We then expanded the cohort to 179 patients (expanded cohort) and also included a confirmatory cohort (49 patients) focusing on SNV 1199G>A. Median OS for G/G versus A/G plus A/A was 15.7 and 11.5 months, respectively ( $p=0.085$ ) for the expanded cohort and 13.8 versus 16.8 months ( $p=0.19$ ) for the confirmatory. In conclusion, in patients with GBM receiving RCT with TMZ, no correlation with survival was found for the SNV:s 1236C>T, 2677G>T/A, and 3435C>T of ABCB1. Although the SNV 1199G>A might have some impact, a clinically significant role could not be confirmed.

Journal Title: The pharmacogenomics journal

PUBMED ID: 31613986

DOI: doi.org/10.1002/ijc.32734

Titolo: Favorable prognosis in pediatric brainstem low-grade glioma: Report from the German SIOP-LGG 2004 cohort.

Autori: Holzapfel J., Kandels D., Schmidt R., Pietsch T., Warmuth-Metz M., Bion B., Krauss J., Kortmann RD., Timmermann B., Thomale UW., Albert MH., Hernáiz Driever P., Witt O., Gnekow AK.

Data di Pubblicazione: 2019-10-16

Abstract: Reports on pediatric low-grade glioma (LGG) of the caudal brainstem are retrospective with heterogeneous cohorts, variable treatments and inconsistent outcome data. We analyzed their natural history and asked whether brainstem location proved unfavorable for survival within the framework of the comprehensive SIOP-LGG 2004 management strategy. Within the prospectively registered, population-based German SIOP-LGG 2004 cohort 116 patients (age 0.2-16.5 years, 10% Neurofibromatosis NF1) were diagnosed with LGG of the pons (27%) and medulla oblongata (73%). After biopsy (23%), variable resection (63%) or radiologic diagnosis only (14%), 59 patients received no adjuvant treatment. Radiologic progression or severe neurologic symptoms prompted chemotherapy (n = 39) or radiotherapy (n = 18). After further progression (28/57), salvage treatments included multiple treatment lines for 12/28 patients. Five-years event-free survival dropped to 0.40, while 5-years overall survival was 0.95 (median observation time 6.8 years). Higher extent of resection yielded lower progression rate (p = 0.001), but at a cost of 21/100 patients suffering from new postsurgical complications including respiratory insufficiency. Central review confirmed pilocytic astrocytoma (56%), diffuse astrocytoma (8%) or glioneuronal histology (16%) (others 4%, no histology 17%). Malignant evolution was documented in five patients associated with Histone3 mutation in 2/5. Our treatment algorithm conveyed high overall survival for pediatric brainstem LGG. Extensive neurosurgical resection did increase additional postoperative neurologic deficits but not overall survival in this often-chronic disease. More than half of all patients can be safely followed by observation, while multimodal adjuvant treatment can control progressive tumors. Molecular assessment should confirm low-grade diagnosis and may detect patterns prognostic for malignant evolution.

Journal Title: International journal of cancer

PUBMED ID: 31595663

DOI: doi.org/10.1002/pbc.28032

Titolo: Phase II study of temozolomide and topotecan (TOTEM) in children with relapsed or refractory extracranial and central nervous system tumors including medulloblastoma with post hoc Bayesian analysis: A European ITCC study

Autori: Le Teuff G., Castaneda-Heredia A., Dufour C., Jaspan T., Calmon R., Devos A., McHugh K., Leblond P., Frappaz D., Aerts I., Zwaan CM., Ducassou S., Chastagner P., Verschuur A., Corradini N., Casanova M., Rubie H., Riccardi R., Le Deley MC., Vassal G., Geoerger B., Geoerger B.

Data di Pubblicazione: 2019-10-10

Abstract: Temozolomide-topotecan results in significant ORR in children with recurrent and refractory medulloblastoma with a favorable toxicity profile.

Journal Title: Pediatric blood & cancer

PUBMED ID: 31568700

DOI: doi.org/10.1002/cam4.2583

Titolo: MIR155HG is a prognostic biomarker and associated with immune infiltration and immune checkpoint molecules expression in multiple cancers.

Autori: Peng L., Chen Z., Chen Y., Wang X., Tang N.

Data di Pubblicazione: 2019-10-1

Abstract: In recent years, immune checkpoint inhibitor has achieved remarkable success in multiple cancer treatment. However, how to pre-judge which patients are suitable for immune checkpoint inhibitor is a difficult problem. We use the existing public bioinformatics database to comprehensively analyze the relationship between clinical data of various cancers with immune checkpoint blocking molecules and long non-coding RNAs (lncRNAs), and try to find the potential predictive value of lncRNA for immunotherapy with checkpoint i

nhibitors. In this study, we found that: (a) high expression of lncRNA MIR155 host gene (MIR155HG) was closely related to better overall survival (OS) in cholangiocarcinoma (CHOL), lung adenocarcinoma (LUAD), and skin cutaneous melanoma (SKCM), and have better disease-free survival (DFS) in CHOL. Meanwhile, the high level of MIR155HG was associated with poorer OS in glioblastoma multiforme (GBM), kidney renal clear cell carcinoma (KIRC), brain lower grade glioma (LGG), and uveal melanoma (UVM). (b) The expression of MIR155HG was significantly correlated with infiltrating levels of immune cells and immune molecules, especially with immune checkpoint molecules such as programmed cell death protein 1 (PD-1), PD-1 ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA4) in most kinds of cancers. (c) Detection of clinical CHOL and liver hepatocellular carcinoma tissues confirmed that there was a strong positive correlation between MIR155HG expression and the levels of CTLA4 and PD-L1. MIR155 host gene can be used as a prognostic marker in multiple cancers, and of great value in predicting the curative effect of immune checkpoint inhibitor therapy owing to it is closely related with immune cells infiltration and immune checkpoint molecules expression.  
Journal Title: Cancer medicine

PUBMED ID: 31561219  
DOI: doi.org/10.3171/2019.6.JNS19409  
Titolo: Impact of facility type and volume in low-grade glioma outcomes.  
Autori: Zhu P., Du XL., Blanco AI., Ballester LY., Tandon N., Berger MS., Zhu JJ., Esquenazi Y.  
Data di Pubblicazione: 2019-9-28  
Abstract: This study provides evidence of survival benefits among LGG patients treated at HVFs and ACs. An increased likelihood of undergoing resections, receiving adjuvant therapies, having shorter LOSs, and the multidisciplinary environment typically found at ACs and HVFs are important contributors to the authors' finding.  
Journal Title: Journal of neurosurgery

PUBMED ID: 31556015  
DOI: doi.org/10.1007/s11060-019-03277-x  
Titolo: Efficacy of initial temozolomide for high-risk low grade gliomas in a phase II AINO (Italian Association for Neuro-Oncology) study: a post-hoc analysis within molecular subgroups of WHO 2016.  
Autori: Rudà R., Pellerino A., Pace A., Carapella CM., Dealis C., Caroli M., Faedi M., Bello L., Migliore E., Marchese G., Bertero L., Cassoni P., Soffietti R.  
Data di Pubblicazione: 2019-9-27  
Abstract: The beneficial effects of initial temozolomide prevail in oligodendrogliomas IDH-mutant and 1p/19q codeleted: thus, these tumors, when incompletely resected or progressive after surgery alone, or with intractable seizures, should receive temozolomide as initial treatment with salvage radiotherapy and/or reoperation and/or second-line chemotherapy at recurrence.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 31527881  
DOI: doi.org/10.1371/journal.pcbi.1006789  
Titolo: 3D spatial organization and network-guided comparison of mutation profiles in Glioblastoma reveals similarities across patients.  
Autori: Dincer C., Kaya T., Keskin O., Gursoy A., Tuncbag N.  
Data di Pubblicazione: 2019-9-19  
Abstract: Glioblastoma multiforme (GBM) is the most aggressive type of brain tumor. Molecular heterogeneity is a hallmark of GBM tumors that is a barrier in developing treatment strategies. In this study, we used the nonsynonymous

mutations of GBM tumors deposited in The Cancer Genome Atlas (TCGA) and applied a systems level approach based on biophysical characteristics of mutations and their organization in patient-specific subnetworks to reduce inter-patient heterogeneity and to gain potential clinically relevant insights. Approximately 10% of the mutations are located in "patches" which are defined as the set of residues spatially in close proximity that are mutated across multiple patients. Grouping mutations as 3D patches reduces the heterogeneity across patients. There are multiple patches that are relatively small in oncogenes, whereas there are a small number of very large patches in tumor suppressors. Additionally, different patches in the same protein are often located at different domains that can mediate different functions. We stratified the patients into five groups based on their potentially affected pathways that are revealed from the patient-specific subnetworks. These subnetworks were constructed by integrating mutation profiles of the patients with the interactome data. Network-guided clustering showed significant association between the groups and patient survival (P-value = 0.0408). Also, each group carries a set of signature 3D mutation patches that affect predominant pathways. We integrated drug sensitivity data of GBM cell lines with the mutation patches and the patient groups to analyze the possible therapeutic outcome of these patches. We found that Pazopanib might be effective in Group 3 by targeting CSF1R. Additionally, inhibiting ATM that is a mediator of PTEN phosphorylation may be ineffective in Group 2. We believe that from mutations to networks and eventually to clinical and therapeutic data, this study provides a novel perspective in the network-guided precision medicine.

Journal Title: PLoS computational biology

PUBMED ID: 31521589

DOI: doi.org/10.1016/j.jgo.2019.08.014

Titolo: Failure to complete standard radiation therapy in glioblastoma patients: Patterns from a national database with implications for survival and therapeutic decision making in older glioblastoma patients.

Autori: Burton E., Yusuf M., Gilbert MR., Gaskins J., Woo S.

Data di Pubblicazione: 2019-9-16

Abstract: Failure to complete standard chemoradiation was associated with decreased survival in our cohort. Patients with risk factors for failure (like advanced age) should be considered for alternative treatments such as hypofractionated radiotherapy.

Journal Title: Journal of geriatric oncology

PUBMED ID: 31515159

DOI: doi.org/10.1016/j.jfma.2019.08.024

Titolo: Clinical implications of multiple glioblastomas: An analysis of prognostic factors and survival to distinguish from their single counterparts.

Autori: Shieh LT., Guo HR., Chang YK., Lu NM., Ho SY.

Data di Pubblicazione: 2019-9-14

Abstract: Patients with multiple GBMs had worse survival compared to those with single GBM. GBM patients without post-operative radiotherapy were also a predictor of worse survival.

Journal Title: Journal of the Formosan Medical Association = Taiwan yi zhi

PUBMED ID: 31514200

DOI: doi.org/10.1159/000502483

Titolo: Open-Label Phase II Evaluation of Imatinib in Primary Inoperable or Incompletely Resected and Recurrent Glioblastoma.

Autori: Sautter L., Hofheinz R., Tuettenberg J., Grimm M., Vajkoczy P., Groden C., Schmieder K., Hochhaus A., Wenz F., Giordano FA.

Data di Pubblicazione: 2019-9-13

Abstract: Imatinib showed no measurable activity in patients with newly diagnosed or recurrent glioblastoma.  
Journal Title: Oncology

PUBMED ID: 31512390

DOI: doi.org/10.1002/pbc.27972

Titolo: Tumor bed proton irradiation in young children with localized medulloblastoma.

Autori: Grewal AS., Li Y., Fisher MJ., Minturn J., Paltin I., Belasco J., Phillips P., Kang T., Lustig RA., Hill-Kayser C.

Data di Pubblicazione: 2019-9-13

Abstract: Five-year OS and RFS following tumor bed irradiation in young children with medulloblastoma appear to be improved compared with other studies that forego the use of radiation therapy in this patient population. This approach should be further investigated in young children with medulloblastoma.

Journal Title: Pediatric blood & cancer

PUBMED ID: 31502042

DOI: doi.org/10.1007/s11060-019-03286-w

Titolo: CBX3 promotes glioma U87 cell proliferation and predicts an unfavorable prognosis.

Autori: Zhao SP., Wang F., Yang M., Wang XY., Jin CL., Ji QK., Li S., Zhao XL.

Data di Pubblicazione: 2019-9-11

Abstract: In the present study, CBX3 was demonstrated to be highly expressed in human glioma tissues, and high CBX3 expression predicted the dismal recurrence-free survival (RFS) and poor overall survival (OS) for glioma patients. High CBX3 expression was dependent on the tumor size, Karnofsky performance scale (KPS) score, WHO grade, recurrence and survival status. Moreover, CBX3 expression knockdown could remarkably suppress the proliferation and colony formation ability of U87 cells, which was achieved through blocking cell arrest at G0/G1 phase and inducing apoptosis. Additionally, our findings also suggested that, compared with shRNA-Ctrl transfection, the mRNA and protein expression levels of CDKN1A have been dramatically up-regulated in vitro after transfection with shRNA-CBX3. Consistent with the results of in vitro assays, the outcomes of xenograft assay and immunohistochemistry (IHC) also indicated that, the tumor growth and Ki-67 expression level were restrained in response to CBX3 inhibition, while the CDKN1A expression level in vivo was up-regulated. Down-regulation of CDKN1A expression partially restored the ability of cell proliferation in the U87 cells, which was inhibited by shRNA-CBX3. CONCLUSIONS: In conclusion, results of the current research suggest that a high CBX3 expression level predicts the poor prognosis for glioma patients. CBX3 can stimulate the growth of glioma U87 cells through targeting CDKN1A and CBX3 may become a novel target in the clinical treatment for glioma.

Journal Title: Journal of neuro-oncology

PUBMED ID: 31480064

DOI: doi.org/10.1159/000501913

Titolo: Medulloblastoma: Distinctive Histo-Molecular Correlation with Clinical Profile, Radiologic Characteristics, and Surgical Outcome.

Autori: Narayan V., Sugur H., Jaiswal J., Arvinda HR., Arivazhagan A., Soman S., Santosh V.

Data di Pubblicazione: 2019-9-4

Abstract: Majority of the patients were pediatric in the study. Age, hemispheric location of tumor, extent of resection, and adjuvant treatment status were the important clinical prognostic factors for survival. Surgery for MB i



s formidable, and VPS can be considered in persistent symptomatic and progressive HCP. Our study on pediatric and adult MB validates the prognostic significance of various clinical, radiologic, and histo-molecular parameters of MB.

Journal Title: Pediatric neurosurgery

PUBMED ID: 31468270

DOI: doi.org/10.1007/s11060-019-03272-2

Titolo: Re-irradiation for children with recurrent medulloblastoma in Toronto, Canada: a 20-year experience.

Autori: Tsang DS., Sarhan N., Ramaswamy V., Nobre L., Yee R., Taylor MD., Hawkins C., Bartels U., Huang A., Tabori U., Hodgson DC., Bouffet E., Laperriere N.

Data di Pubblicazione: 2019-8-31

Abstract: Re-irradiation for recurrent pediatric medulloblastoma can offer some patients disease control, particularly those with focally recurrent disease in the brain. Prospective studies are needed to confirm subgroups of patients who may benefit most from RT2.

Journal Title: Journal of neuro-oncology

PUBMED ID: 31435963

DOI: doi.org/10.1111/bpa.12782

Titolo: Clinical relevance of molecular subgrouping of gliomatosis cerebri per 2016 WHO classification: a clinicopathological study of 89 cases.

Autori: Kwon MJ., Kang SY., Cho H., Lee JI., Kim ST., Suh YL.

Data di Pubblicazione: 2019-8-23

Abstract: The extremely invasive phenotypes and genotypes related to progression of gliomatosis cerebri (GC) remain unclear although GC has been removed as an independent entity from the 2016 WHO classification. Hence, categorization of GC under the current WHO molecular classification is essential, and the molecular subgroups that might contribute to GC progression should be compared with the histopathological differences between initial and new lesions identified during follow-up. Analyses of IDH1/2 and TERTp mutations and 1p/19q co-deletion, and immunohistochemistry of IDH1-R132H, ATRX, p53 and galectin-3 were performed. Anaplastic astrocytoma, IDH-wildtype (AA-IDHwt) was the common molecular subgroup (52.8%), followed by diffuse astrocytoma, IDH-wildtype (DA-IDHwt) and AA, IDH-mutant (AA-IDHmt) (each 16.9%), DA-IDHmt (7.9%), glioblastoma (GBM)-IDHwt (3.3%) and GBM-IDHmt (2.2%). Approximately 92% of the AA-IDHwt lesions progressed to histologically confirmed GBM in the newly enhanced lesions harboring the TERTp mutation and expressing galectin-3. Similar to primary GBMs, GC-related GBMs that progressed from the IDHwt subgroups showed microvascular proliferation, palisading necrosis or thrombotic occlusion, implying that a subset of IDHwt subgroups may evolve to overt GBM. Molecular subgrouping did not provide the perfect prediction for the survival of GC patients. The AA-IDHwt group showed worse overall and progression-free survival (PFS) than the AA-IDHmt group. Biopsy plus radiotherapy, chemotherapy and temozolomide treatment for DA-IDHwt, and resection plus radiotherapy and temozolomide treatment for AA-IDHwt prolonged PFS. In conclusions, majority of GC was of the AA-IDHwt subgroup, which progressed to GBM. Molecular subgroups may assist in the selection of treatment modalities, because "GC pattern" still remains as a special growth of gliomas in WHO 2016 classification without established treatment guideline.

Journal Title: Brain pathology (Zurich, Switzerland)

PUBMED ID: 31435824

DOI: doi.org/10.1007/s00701-019-04039-4

Titolo: Spectroscopic measurement of 5-ALA-induced intracellular protoporphyrin IX in pediatric brain tumors.

Autori: Schwake M., Kaneko S., Suero Molina E., Müther M., Schipmann S., Köchling M., Brentrup A., Stummer W.

Data di Pubblicazione: 2019-8-23

Abstract: We demonstrate a strong association between intraoperative observations and spectrometric measurements of PPIX fluorescence in tumor tissue. As in former studies, fluorescence signal was more commonly observed in malignant glial tumors. Further prospective controlled trials should be conducted to investigate the feasibility of 5-ALA-guided resection of pediatric brain tumors.

Journal Title: Acta neurochirurgica

PUBMED ID: 31427235

DOI: doi.org/10.1016/j.jocn.2019.08.039

Titolo: Pretreatment intratumoral susceptibility signals correlate with response to high-dose methotrexate and progression-free survival in primary central nervous system lymphoma.

Autori: Deguchi S., Nakashima K., Muramatsu K., Mitsuya K., Oishi T., Shirata K., Hayashi N., Sugino T., Endo M., Nakasu Y.

Data di Pubblicazione: 2019-8-21

Abstract: We aimed to estimate the frequency of intratumoral susceptibility signals (ITSS) in susceptibility-weighted imaging (SWI) in consecutive patients with primary central nervous system lymphoma (PCNSL), and to determine if pretreatment heterogeneity of PCNSL is predictive of response to chemotherapy by using ITSS on SWI. We retrospectively examined 29 immunocompetent patients with PCNSL who underwent SWI-MRI before treatment. A univariate analysis was conducted with Fisher's exact test. Progression free survival (PFS) was calculated by the Kaplan-Meier method and compared by the log rank test. The patients, including 16 males, were initially treated at a median age of 69 years. All tissue types were diffuse large B-cell lymphoma. Nineteen patients (66%) presented lesions with ITSS. Sixteen patients (55%) received initial treatment with R-MTX (rituximab plus high-dose methotrexate). Seven out of nine patients with ITSS exhibited a poor response, whereas all seven without ITSS exhibited a good response to R-MTX. Regarding the absence of ITSS, the sensitivity, specificity, and diagnostic accuracy for a good response to R-MTX were 0.78, 1.00, and 0.88, respectively. Patients without ITSS showed significantly longer PFS compared to patients with ITSS (median PFS: 28.9 vs 2.1 months,  $P < 0.01$ ). In conclusion, ITSS in PCNSL patients were more common than previously reported. We have to be careful to use ITSS for differentiating PCNSL and glioblastoma. Presence of ITSS correlated significantly with therapeutic response to R-MTX. ITSS may be a new marker for the response to chemotherapy in patients with PCNSL. A prospective multi-institutional analysis is needed.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 31400262

DOI: doi.org/10.2174/0929867326666190809221332

Titolo: Phytochemical-Mediated Glioma Targeted Treatment: Drug Resistance and Novel Delivery Systems.

Autori: Cao H., Li X., Wang F., Zhang Y., Xiong Y., Yang Q.

Data di Pubblicazione: 2019-8-11

Abstract: Glioma, especially its most malignant type, Glioblastoma (GBM), is the most common and the most aggressive malignant tumour in the central nervous system. Currently, we have no specific therapies that can significantly improve its dismal prognosis. Recent studies have reported promising in vitro

o experimental results of several novel glioma-targeting drugs; these studies are encouraging to both researchers and patients. However, clinical trials have revealed that novel compounds that focus on a single, clear glioma genetic alteration may not achieve a satisfactory outcome or have side effects that are unbearable. Based on this consensus, phytochemicals that exhibit multiple bioactivities have recently attracted much attention. Traditional Chinese medicine and traditional Indian medicine (Ayurveda) have shown that phytochemicals inhibit glioma angiogenesis, cancer stem cells and tumour proliferation; these results suggest a novel drug therapeutic strategy. However, single phytochemicals or their direct usage may not reverse comprehensive malignancy due to poor histological penetrability or relatively unsatisfactory in vivo efficiency. Recent research that has employed temozolomide combination treatment and Nanoparticles (NPs) with phytochemicals has revealed a powerful dual-target therapy and a high blood-brain barrier penetrability, which is accompanied by low side effects and strong specific targeting. This review is focused on major phytochemicals that have contributed to glioma-targeting treatment in recent years and their role in drug resistance inhibition, as well as novel drug delivery systems for clinical strategies. Lastly, we summarize a possible research strategy for the future.

Journal Title: Current medicinal chemistry

PUBMED ID: 31397594

DOI: doi.org/10.1080/09537104.2019.1652263

Titolo: Fondaparinux cross-reactivity in heparin-induced thrombocytopenia successfully treated with high-dose intravenous immunoglobulin and rivaroxaban.

Autori: Manji F., Warkentin TE., Sheppard JI., Lee A.

Data di Pubblicazione: 2019-8-10

Abstract: HIT, a prothrombotic disorder caused by heparin-dependent antibodies, is often treated with fondaparinux, usually with good outcomes. A 70-year-old female developed severe HIT (platelet count,  $25 \times 10^9$ ).

Journal Title: Platelets

PUBMED ID: 31392595

DOI: doi.org/10.1007/s11060-019-03227-7

Titolo: Phase I/II study of bevacizumab with BKM120, an oral PI3K inhibitor, in patients with refractory solid tumors (phase I) and relapsed/refractory glioblastoma (phase II).

Autori: Hainsworth JD., Becker KP., Mekhail T., Chowdhary SA., Eakle JF., Wright D., Langdon RM., Yost KJ., Padula GDA., West-Osterfield K., Scarberry M., Shaifer CA., Shastry M., Burris HA., Shih K.

Data di Pubblicazione: 2019-8-9

Abstract: The efficacy seen in this study is similar to the efficacy previously reported with single-agent bevacizumab. This regimen was poorly tolerated, despite the low daily dose of BKM120. Further development of this combination for the treatment of glioblastoma is not recommended.

Journal Title: Journal of neuro-oncology

PUBMED ID: 31386038

DOI: doi.org/10.1093/nop/npy019

Titolo: Re-irradiation for recurrent high-grade gliomas: a systematic review and analysis of treatment technique with respect to survival and risk of radionecrosis.

Autori: Shanker M., Chua B., Bettington C., Foote MC., Pinkham MB.

Data di Pubblicazione: 2019-8-7

Abstract: The published literature suggests that OS is highest after re-irradiation using SRS, followed by FSRT and conventionally fractionated radiotherapy.

rapy. Whether this represents superiority of the treatment technique or an uncontrolled selection bias is uncertain. The risk of radionecrosis was low for all modalities overall. Re-irradiation is a feasible option in appropriately selected patients.

Journal Title: Neuro-oncology practice

PUBMED ID: 31369680

DOI: doi.org/10.1093/neuonc/noz131

Titolo: Temporal muscle thickness is an independent prognostic marker in patients with progressive glioblastoma: translational imaging analysis of the EORTC 26101 trial.

Autori: Furtner J., Genbrugge E., Gorlia T., Bendszus M., Nowosielski M., Gollfinopoulos V., Weller M., van den Bent MJ., Wick W., Preusser M.

Data di Pubblicazione: 2019-8-2

Abstract: Reduced TMT is an independent negative prognostic parameter in patients with progressive glioblastoma and may help to facilitate patient management by supporting patient stratification for therapeutic interventions or clinical trials.

Journal Title: Neuro-oncology

PUBMED ID: 31363920

DOI: doi.org/10.1007/s00701-019-04007-y

Titolo: Intraoperative fluorescence diagnosis in the brain: a systematic review and suggestions for future standards on reporting diagnostic accuracy and clinical utility.

Autori: Stummer W., Koch R., Valle RD., Roberts DW., Sanai N., Kalkanis S., Hadjipanayis CG., Suero Molina E.

Data di Pubblicazione: 2019-8-1

Abstract: Detailed, transparent, and uniform reporting on diagnostic accuracy of intraoperative imaging methods is necessary. In the absence of such reporting, studies will not be comparable or reproducible. Future studies should consider some of the recommendations given here.

Journal Title: Acta neurochirurgica

PUBMED ID: 31362788

DOI: doi.org/10.1186/s40478-019-0773-8

Titolo: Phase I and phase II sonidegib and vismodegib clinical trials for the treatment of paediatric and adult MB patients: a systemic review and meta-analysis.

Autori: Li Y., Song Q., Day BW.

Data di Pubblicazione: 2019-8-1

Abstract: Sonidegib and vismodegib were well tolerated and demonstrated anti-tumour activity in SHH-driven paediatric and adult MB by effectively inhibiting Hh signalling. These results support the ongoing clinical trials using SMO inhibitors in combination with conventional chemotherapies for the treatment of relapsed MB

Journal Title: Acta neuropathologica communications

PUBMED ID: 31360809

DOI: doi.org/10.1016/j.adro.2019.03.009

Titolo: Role of Radiation Therapy in the Management of Diffuse Intrinsic Pontine Glioma: A Systematic Review.

Autori: Gallitto M., Lazarev S., Wasserman I., Stafford JM., Wolden SL., Termezakis SA., Bindra RS., Bakst RL.

Data di Pubblicazione: 2019-7-31

Abstract: As one of the largest systematic reviews examining RT for DIPG, this report may serve as a useful tool to help clinicians choose the most appropriate treatment approach, while also providing a platform for future investigations into the utility of RT and systemic therapy.  
Journal Title: Advances in radiation oncology

PUBMED ID: 31345255

DOI: doi.org/10.1186/s40478-019-0774-7

Titolo: Dramatic response of BRAF V600E-mutant epithelioid glioblastoma to combination therapy with BRAF and MEK inhibitor: establishment and xenograft of a cell line to predict clinical efficacy.

Autori: Kanemaru Y., Natsumeda M., Okada M., Saito R., Kobayashi D., Eda T., Watanabe J., Saito S., Tsukamoto Y., Oishi M., Saito H., Nagahashi M., Sasaki T., Hashizume R., Aoyama H., Wakai T., Kakita A., Fujii Y.

Data di Pubblicazione: 2019-7-27

Abstract: Epithelioid glioblastoma is a rare aggressive variant of glioblastoma (GBM) characterized by a dismal prognosis of about 6 months and frequent leptomeningeal dissemination. A recent study has revealed that 50% of epithelioid GBMs harbor three genetic alterations - BRAF V600E mutation, TERT promoter mutations, and homozygous deletions of CDKN2A/2B. Emerging evidence supports the effectiveness of targeted therapies for brain tumors with BRAF V600E mutation. Here we describe a dramatic radiographical response to combined therapy with BRAF and MEK inhibitors in a patient with epithelioid GBM harboring BRAF V600E mutation, characterized by thick spinal dissemination. From relapsed tumor procured at autopsy, we established a cell line retaining the BRAF V600E mutation, TERT promoter mutation and CDKN2A/2B loss. Intracranial implantation of these cells into mice resulted in tumors closely resembling the original, characterized by epithelioid tumor cells and dissemination, and invasion into the perivascular spaces. We then confirmed the efficacy of treatment with BRAF and MEK inhibitor both in vitro and in vivo. Epithelioid GBM with BRAF V600E mutation can be considered a good treatment indication for precision medicine, and this patient-derived cell line should be useful for prediction of the tumor response and clarification of its biological characteristics.

Journal Title: Acta neuropathologica communications

PUBMED ID: 31343422

DOI: doi.org/10.1097/COC.0000000000000564

Titolo: ENvironmental Dynamics Underlying Responsive Extreme Survivors (ENDURES) of Glioblastoma: A Multidisciplinary Team-based, Multifactorial Analytical Approach.

Autori: Johnston SK., Whitmire P., Massey SC., Kumthekar P., Porter AB., Rahunand N., Gonzalez-Cuyar LF., Mrugala MM., Hawkins-Daarud A., Jackson PR., Hu LS., Sarkaria JN., Wang L., Gatenby RA., Egan KM., Canoll P., Swanson KR., Swanson KR.

Data di Pubblicazione: 2019-7-26

Abstract: Although glioblastoma (GBM) is a fatal primary brain cancer with short median survival of 15 months, a small number of patients survive >5 years after diagnosis; they are known as extreme survivors (ES). Because of their rarity, very little is known about what differentiates these outliers from other patients with GBM. For the purpose of identifying unknown drivers of extreme survivorship in GBM, the ENDURES consortium (ENvironmental Dynamics Underlying Responsive Extreme Survivors of GBM) was developed. This consortium is a multicenter collaborative network of investigators focused on the integration of multiple types of clinical data and the creation of patient-specific models of tumor growth informed by radiographic and histologic parameters. Leveraging our combined resources, the goals of the ENDURES consortium

are 2-fold: (1) to build a curated, searchable, multilayered repository housing clinical and outcome data on a large cohort of ES patients with GBM; and (2) to leverage the ENDURES repository for new insights into tumor behavior and novel targets for prolonging survival for all patients with GBM. In this article, the authors review the available literature and discuss what is already known about ES. The authors then describe the creation of their consortium and some preliminary results.

Journal Title: American journal of clinical oncology

PUBMED ID: 31324990

DOI: doi.org/10.1007/s11864-019-0673-y

Titolo: A Second Course of Radiotherapy in Patients with Recurrent Malignant Gliomas: Clinical Data on Re-irradiation, Prognostic Factors, and Usefulness of Digital Biomarkers.

Autori: Straube C., Kessel KA., Zimmer C., Schmidt-Graf F., Schlegel J., Gempt J., Meyer B., Combs SE.

Data di Pubblicazione: 2019-7-21

Abstract: The treatment of malignant gliomas has undergone a significant intensification during the past decade, and the interdisciplinary treatment team has learned that all treatment opportunities, including surgery and radiotherapy (RT), also have a central role in recurrent gliomas. Throughout the decades, re-irradiation (re-RT) has achieved a prominent place in the treatment of recurrent gliomas. A solid body of evidence supports the safety and efficacy of re-RT, especially when modern techniques are used, and justifies the early use of this regimen, especially in the case when macroscopic disease is present. Additionally, a second adjuvant re-RT to the resection cavity is currently being investigated by several investigators and seems to offer promising results. Although advanced RT technologies, such as stereotactic radiosurgery (SRS), fractionated stereotactic radiotherapy (FSRT), intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT) have become available in many centers, re-RT should continue to be kept in experienced hands so that they can select the optimal regimen, the ideal treatment volume, and the appropriate techniques from their tool-boxes. Concomitant or adjuvant use of systemic treatment options should also strongly be taken into consideration, especially because temozolomide (TMZ), cyclohexyl-nitrosourea (CCNU), and bevacizumab have shown a good safety profile; they should be considered, if available. Nonetheless, the selection of patients for re-RT remains crucial. Single factors, such as patient age or the progression-free interval (PFI), fall too short. Therefore, powerful prognostic scores have been generated and validated, and these scores should be used for patient selection and counseling.

Journal Title: Current treatment options in oncology

PUBMED ID: 31323633

DOI: doi.org/10.3171/2019.4.JNS183395

Titolo: To treat or not to treat? A retrospective multicenter assessment of survival in patients with IDH-mutant low-grade glioma based on adjuvant treatment.

Autori: Pala A., Coburger J., Scherer M., Ahmeti H., Roder C., Gessler F., Jungk C., Scheuerle A., Senft C., Tatagiba M., Synowitz M., Wirtz CR., Schmitz B., Unterberg AW.

Data di Pubblicazione: 2019-7-20

Abstract: In this series of IDH-mutated LGGs, adjuvant treatment with RT, CT with temozolomide (TMZ), or the combination of both showed no significant advantage in terms of PFS and OS. Even in high-risk patients, the authors observed a similar significantly negative impact of adjuvant treatment on PFS and OS. These results underscore the importance of a CTR in LGG. Whether patients  $\geq 40$  years old should receive adjuvant treatment despite a CTR should be

a matter of debate. A potential tumor dedifferentiation by administration of early TMZ, RT, or RT+CT in IDH-mutated LGG should be considered. However, these data are limited by the retrospective study design and the potentially heterogeneous indication for adjuvant treatment.  
Journal Title: Journal of neurosurgery

PUBMED ID: 31315671

DOI: doi.org/10.1186/s40425-019-0673-2

Titolo: Diverse immunotherapies can effectively treat syngeneic brainstem tumors in the absence of overt toxicity.

Autori: Schuelke MR., Wongthida P., Thompson J., Kottke T., Driscoll CB., Huffer AL., Shim KG., Coffey M., Pulido J., Evgin L., Vile RG.

Data di Pubblicazione: 2019-7-19

Abstract: It remains imperative to regard the brainstem with caution for immunotherapeutic intervention. Nonetheless, we show that further careful development of immunotherapies for pediatric brainstem tumors is warranted to harness the potential potency of anti-tumor immune responses, despite their possible toxicity within this anatomically sensitive location.

Journal Title: Journal for immunotherapy of cancer

PUBMED ID: 31297242

DOI: doi.org/10.1136/esmoopen-2019-000520

Titolo: How we treat glioblastoma.

Autori: Weller M., Le Rhun E., Preusser M., Tonn JC., Roth P.

Data di Pubblicazione: 2019-7-13

Abstract: Glioblastoma is an intrinsic brain tumour thought to arise from neuroglial progenitor cells. Its incidence increases steadily with age. Males are moderately more often affected. Genetic predisposition and exposure to irradiation in childhood are the only established risk factors which, however, account only for a very small proportion of glioblastomas. Surgery as safely feasible not only to allow for tissue diagnosis but also to reduce tumour volume is usually the first therapeutic measure. Radiotherapy delivered to the tumour region with a safety margin has been demonstrated to roughly double survival four decades ago. Temozolomide given during radiotherapy followed by six cycles of maintenance chemotherapy was the first and so far only pharmacological treatment shown to prolong survival. Adding tumour-treating fields during maintenance, temozolomide chemotherapy has been reported to prolong survival. There is little evidence that any intervention at relapse improves outcome, but nitrosourea-based chemotherapy, commonly lomustine, is probably the most agreed on standard of care. Bevacizumab prolongs progression-free survival and probably quality of life in the first line or recurrent setting, but not overall survival, and is therefore not approved in the European Union. Immunotherapy remains experimental. Drugs in advanced clinical development include the programmed death 1 antibody, nivolumab, the antibody drug conjugate depatuxizumab directed to the epidermal growth factor receptor and the proteasome inhibitor marizomib.

Journal Title: ESMO open

PUBMED ID: 31292802

DOI: doi.org/10.1007/s11060-019-03236-6

Titolo: Phase II study of Dovitinib in recurrent glioblastoma.

Autori: Sharma M., Schilero C., Peereboom DM., Hobbs BP., Elson P., Stevens GHJ., McCrae K., Nixon AB., Ahluwalia MS.

Data di Pubblicazione: 2019-7-12

Abstract: Dovitinib was not efficacious in prolonging the PFS in patients with recurrent GBM irrespective of prior treatment with anti-angiogenic therapy (including bevacizumab).

Journal Title: Journal of neuro-oncology

PUBMED ID: 31273578

DOI: doi.org/10.1007/s11060-019-03223-x

Titolo: Phase II study of weekly carboplatin in pretreated adult malignant gliomas.

Autori: Villani V., Pace A., Vidiri A., Tanzilli A., Sperati F., Terrenato I., Mariantonia C., Casini B., Metro G., Maschio M., Tatiana K., Cognetti F., Fabi A.

Data di Pubblicazione: 2019-7-6

Abstract: Our findings show that single agent, weekly, intravenous administration of carboplatin may have a role in patients with recurrent glioma and suggest that pre-treatment with corticosteroids may confer survival benefit.

Journal Title: Journal of neuro-oncology

PUBMED ID: 31243619

DOI: doi.org/10.1007/s10633-019-09703-9

Titolo: Central and peripheral steady-state visual evoked potentials in children with optic pathway gliomas.

Autori: Rassi SZ., Ospina LH., Bochereau A., Samson Y., Perreault S., Saint-Amour D.

Data di Pubblicazione: 2019-6-28

Abstract: Steady-state visual evoked potentials could eventually be implemented in the clinical assessment and follow-up of central visual field deficits in uncooperative or nonverbal children but seem to have limited usefulness for evaluation of peripheral visual field deficits. Additional studies are needed to identify testing parameters for full visual field assessment.

Journal Title: Documenta ophthalmologica. Advances in ophthalmology

PUBMED ID: 31236820

DOI: doi.org/10.1007/s11060-019-03225-9

Titolo: Outcomes of salvage re-irradiation in recurrent medulloblastoma correlate with age at initial diagnosis, primary risk-stratification, and molecular subgrouping.

Autori: Gupta T., Maitre M., Sastri GJ., Krishnatry R., Shirsat N., Epari S., Sahay A., Chinnaswamy G., Patil V., Shetty P., Moiyadi A.

Data di Pubblicazione: 2019-6-26

Abstract: Salvage re-RT provides good local control and encouraging survival outcomes with acceptable toxicity in selected patients with recurrent/progressive MB.

Journal Title: Journal of neuro-oncology

PUBMED ID: 31225627

DOI: doi.org/10.1093/neuros/nyz212

Titolo: ABC Transporter Inhibition Plus Dexamethasone Enhances the Efficacy of Convection Enhanced Delivery in H3.3K27M Mutant Diffuse Intrinsic Pontine Glioma.

Autori: Tsvankin V., Hashizume R., Katagi H., Herndon JE., Lascola C., Venkatraman TN., Picard D., Burrus B., Becher OJ., Thompson EM.

Data di Pubblicazione: 2019-6-22

Abstract: ABC transporter inhibition plus dexamethasone enhances the efficacy of CED dasatinib, resulting in enhanced tumor cellular apoptosis and improved survival in H3.3K27M mutant DIPG.

Journal Title: Neurosurgery



PUBMED ID: 31203194

DOI: doi.org/10.1016/j.ejca.2019.05.012

Titolo: The added value of health-related quality of life as a prognostic indicator of overall survival and progression-free survival in glioma patients : a meta-analysis based on individual patient data from randomised controlled trials.

Autori: Coomans M., Dirven L., K Aaronson N., Baumert BG., van den Bent M., Bottomley A., Brandes AA., Chinot O., Coens C., Gorlia T., Herrlinger U., Kime-Guibert F., Malmström A., Martinelli F., Stupp R., Talacchi A., Weller M., Wick W., Reijneveld JC., Taphoorn MJB., Taphoorn MJB.

Data di Pubblicazione: 2019-6-17

Abstract: Our findings demonstrate that several baseline HRQoL variables are independently prognostic for OS and PFS, yet the added value of HRQoL to the known clinical prognostic variables was small.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 31170245

DOI: doi.org/10.1371/journal.pone.0217881

Titolo: Hypofractionated radiation therapy and temozolomide in patients with glioblastoma and poor prognostic factors. A prospective, single-institution experience.

Autori: Jablonska PA., Diez-Valle R., Pérez-Larraya JG., Moreno-Jiménez M., Idoate MÁ., Arbea L., Tejada S., Garcia de Eulate MR., Ramos L., Arbizu J., Domínguez P., Aristu JJ.

Data di Pubblicazione: 2019-6-7

Abstract: Patients with poor clinical factors other than advanced age can be selected for hypofractionated radiotherapy. The OS and PFS rates obtained in our series are similar to those in patients treated with standard fractionation, assuring good treatment adherence, low rates of toxicity and probable improved cost-effectiveness.

Journal Title: PloS one

PUBMED ID: 31154523

DOI: doi.org/10.1007/s00280-019-03879-2

Titolo: Safety, tolerability, and pharmacokinetics of anti-EGFRvIII antibody-drug conjugate AMG 595 in patients with recurrent malignant glioma expressing EGFRvIII.

Autori: Rosenthal M., Curry R., Reardon DA., Rasmussen E., Upreti VV., Damera MA., Henary HA., Hill JS., Cloughesy T.

Data di Pubblicazione: 2019-6-3

Abstract: AMG 595 exhibited favorable pharmacokinetics and is a unique therapy with possible benefit for some patients with EGFRvIII-mutated GBM with limited therapeutic options.

Journal Title: Cancer chemotherapy and pharmacology

PUBMED ID: 31124566

DOI: doi.org/10.1093/annonc/mdz164

Titolo: Molecular pathology of tumors of the central nervous system.

Autori: Kristensen BW., Priesterbach-Ackley LP., Petersen JK., Wesseling P.

Data di Pubblicazione: 2019-5-25

Abstract: Since the update of the 4th edition of the WHO Classification of Central Nervous System (CNS) Tumors published in 2016, particular molecular characteristics are part of the definition of a subset of these neoplasms. This combined 'histo-molecular' approach allows for a much more precise diagnosis of especially diffuse gliomas and embryonal CNS tumors. This review provides an update of the most important diagnostic and prognostic markers for state-of-the-art diagnosis of primary CNS tumors. Defining molecular markers

for diffuse gliomas are IDH1/IDH2 mutations, 1p/19q codeletion and mutations in histone H3 genes. Medulloblastomas, the most frequent embryonal CNS tumors, are divided into four molecularly defined groups according to the WHO 2016 Classification: wingless/integrated (WNT) signaling pathway activated, sonic hedgehog (SHH) signaling pathway activated and tumor protein p53 gene (TP53)-mutant, SHH-activated and TP53-wildtype, and non-WNT/non-SHH-activated. Molecular characteristics are also important for the diagnosis of several other CNS tumors, such as RELA fusion-positive subtype of ependymoma, atypical teratoid rhabdoid tumor (AT/RT), embryonal tumor with multilayered rosettes, and solitary fibrous tumor/hemangiopericytoma. Immunohistochemistry is a helpful alternative for further molecular characterization of several of these tumors. Additionally, genome-wide methylation profiling is a very promising new tool in CNS tumor diagnostics. Much progress has thus been made by translating the most relevant molecular knowledge into a more precise clinical diagnosis of CNS tumors. Hopefully, this will enable more specific and more effective therapeutic approaches for the patients suffering from these tumors. Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 31119479

DOI: doi.org/10.1007/s11060-019-03194-z

Titolo: Phase I-II trial of imatinib mesylate (Gleevec; STI571) in treatment of recurrent oligodendroglioma and mixed oligoastrocytoma. North central cancer treatment group study N0272 (ALLIANCE/NCCTG).

Autori: Jaeckle KA., Anderson SK., Twohy EL., Dixon JG., Giannini C., Jenkins R., Egorin MJ., Sarkaria JN., Brown PD., Flynn PJ., Schwerkoske J., Buckner JC., Galanis E.

Data di Pubblicazione: 2019-5-24

Abstract: Although adequate plasma levels were achieved, the observed PFS6 of 33% did not reach our pre-defined threshold for success. Although OS was longer in imatinib-treated patients than controls, this finding would require forward validation in a larger cohort. Imatinib might show greater activity in a population enriched for PDGF-dependent pathway activation in tumor tissue.

Journal Title: Journal of neuro-oncology

PUBMED ID: 31113843

DOI: doi.org/10.1158/1078-0432.CCR-18-3850

Titolo: Overall Survival in Malignant Glioma Is Significantly Prolonged by Neurosurgical Delivery of Etoposide and Temozolomide from a Thermo-Responsive Biodegradable Paste.

Autori: Smith SJ., Tyler BM., Gould T., Veal GJ., Gorelick N., Rowlinson J., Serra R., Ritchie A., Berry P., Otto A., Choi J., Skuli N., Estevez-Cebrero M., Shakesheff KM., Brem H., Grundy RG., Rahman R.

Data di Pubblicazione: 2019-5-23

Abstract: The significant survival benefit of intracavity chemotherapy demonstrates clinical applicability of PLGA/PEG paste-mediated delivery of temozolomide and etoposide adjuvant to radiotherapy. PLGA/PEG paste offers a future platform for combination delivery of molecular targeted compounds.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 31109839

DOI: doi.org/10.1016/j.canrad.2018.05.008

Titolo: Twenty years experience in treating childhood medulloblastoma: Between the past and the present.

Autori: Khalil J., Qing Z., Chuanying Z., Belkacémi Y., Benjaafar N., Mawei J.

Data di Pubblicazione: 2019-5-22

Abstract: Overall, our results are comparable to those reported in literature. Nevertheless, efforts should be made to ensure longer follow-ups and correctly assess treatment-related toxicity.

Journal Title: Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique

PUBMED ID: 31089718

DOI: doi.org/10.1093/neuonc/noz071

Titolo: Regorafenib in advanced high-grade glioma: a retrospective bicentric analysis.

Autori: Tzaridis T., Gefner-Tuma I., Hirsch S., Skardelly M., Bender B., Paulsen F., Schaub C., Weller J., Schäfer N., Herrlinger U., Tabatabai G.

Data di Pubblicazione: 2019-5-16

Abstract:

Journal Title: Neuro-oncology

PUBMED ID: 31076534

DOI: doi.org/10.1212/WNL.00000000000007643

Titolo: Imaging necrosis during treatment is associated with worse survival in EORTC 26101 study.

Autori: Nowosielski M., Gorlia T., Bromberg JEC., Sahm F., Harting I., Kickingereder P., Brandes AA., Taphoorn MJB., Taal W., Domont J., Idbaih A., Campone M., Clement PM., Weller M., Fabbro M., Le Rhun E., Platten M., Golfinopoulos V., van den Bent MJ., Bendszus M., Wick W.

Data di Pubblicazione: 2019-5-12

Abstract: Increase of and new development of imaging necrosis during treatment is a negative prognostic factor for patients with progressive glioblastoma. These data call for consideration of integrating the assessment of imaging necrosis as a separate item into the MRI response assessment criteria.

Journal Title: Neurology

PUBMED ID: 31060906

DOI: doi.org/10.1016/j.ebiom.2019.04.043

Titolo: Potent anti-tumor efficacy of palbociclib in treatment-naïve H3.3K27M-mutant diffuse intrinsic pontine glioma.

Autori: Sun Y., Sun Y., Yan K., Li Z., Xu C., Geng Y., Pan C., Chen X., Zhang L., Xi Q.

Data di Pubblicazione: 2019-5-8

Abstract: Our findings thus revealed that palbociclib could be the therapeutic strategy for treatment-naïve DIPG with H3.3K27M mutation. **FUND:** Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support, Beijing Municipal Natural Science Foundation, Ministry of Science and Technology of China, and National Natural Science Foundation of China.

Journal Title: EBioMedicine

PUBMED ID: 31050315

DOI: doi.org/10.1080/13696998.2019.1614933

Titolo: Tumor treating fields and maintenance temozolomide for newly-diagnosed glioblastoma: a cost-effectiveness study.

Autori: Guzauskas GF., Pollom EL., Stieber VW., Wang BCM., Garrison LP.

Data di Pubblicazione: 2019-5-4

Abstract: None

Journal Title: Journal of medical economics

PUBMED ID: 31038851

DOI: doi.org/10.1002/cam4.2192

Titolo: Immune microenvironments differ in immune characteristics and outcome of glioblastoma multiforme.

Autori: Zhang B., Shen R., Cheng S., Feng L.

Data di Pubblicazione: 2019-5-1

Abstract: Understanding the interactions between tumors and the host immune system holds great promise to uncover biomarkers for targeted therapies, predict the prognosis of patients and guide clinical treatment. However, the immune signatures of glioblastoma multiforme (GBM) remain largely unstudied in terms of systematic analyses. We aimed to classify GBM samples according to immune-related genes and complement the existing immunotherapy system knowledge. In this study, we designed a strategy to identify 3 immune subtypes representing 3 different immune microenvironments (M1-M3) and associated with prognosis. The 3 subtypes were significantly different in terms of specific immune characteristics (immune cell subpopulations, immune responses, immune cells, and checkpoint gene interactions). In addition, copy number variations and methylation changes were identified that correlated with genes related to a worse prognosis subtype in the microenvironment. More importantly, in M3 (worst prognosis subtype) and M2 (best prognosis subtype), the interaction between immune cells and checkpoint genes was different, which had an important effect on the prognosis. Finally, we used risk scores of immune cells and checkpoint genes to evaluate the prognosis of GBM patients and validated the results with 3 independent datasets. Disordered interactions between immune cells and checkpoint genes result in a change in the immune microenvironment and affects the prognosis of patients. We propose that a better understanding of the immune microenvironment of advanced cancers may provide new insights into immunotherapy.

Journal Title: Cancer medicine

PUBMED ID: 31036068

DOI: doi.org/10.1186/s40478-019-0714-6

Titolo: Delta-24-RGD combined with radiotherapy exerts a potent antitumor effect in diffuse intrinsic pontine glioma and pediatric high grade glioma models.

Autori: Martinez-Velez N., Marigil M., García-Moure M., Gonzalez-Huarriz M., Aristu JJ., Ramos-García LI., Tejada S., Díez-Valle R., Patiño-García A., Beccher OJ., Gomez-Manzano C., Fueyo J., Alonso MM.

Data di Pubblicazione: 2019-5-1

Abstract: Pediatric high grade gliomas (pHGG), including diffuse intrinsic pontine gliomas (DIPGs), are aggressive tumors with a dismal outcome. Radiotherapy (RT) is part of the standard of care of these tumors; however, radiotherapy only leads to a transient clinical improvement. Delta-24-RGD is a genetically engineered tumor-selective adenovirus that has shown safety and clinical efficacy in adults with recurrent gliomas. In this work, we evaluated the feasibility, safety and therapeutic efficacy of Delta-24-RGD in combination with radiotherapy in pHGGs and DIPGs models. Our results showed that the combination of Delta-24-RGD with radiotherapy was feasible and resulted in a synergistic anti-glioma effect in vitro and in vivo in pHGG and DIPG models. Interestingly, Delta-24-RGD treatment led to the downregulation of relevant DNA damage repair proteins, further sensitizing tumors cells to the effect of radiotherapy. Additionally, Delta-24-RGD/radiotherapy treatment significantly increased the trafficking of immune cells (CD3, CD4+ and CD8+) to the tumor niche compared with single treatments. In summary, administration of the Delta-24-RGD/radiotherapy combination to pHGG and DIPG models is safe and si

gnificantly increases the overall survival of mice bearing these tumors. Our data offer a rationale for the combination Delta-24-RGD/radiotherapy as a therapeutic option for children with these tumors. SIGNIFICANCE: Delta-24-RGD/radiotherapy administration is safe and significantly increases the survival of treated mice. These positive data underscore the urge to translate this approach to the clinical treatment of children with pHGG and DIPGs.

Journal Title: Acta neuropathologica communications

PUBMED ID: 31022591

DOI: doi.org/10.1016/j.ejca.2019.03.019

Titolo: Brainstem biopsy in pediatric diffuse intrinsic pontine glioma in the era of precision medicine: the INFORM study experience.

Autori: Pfaff E., El Damaty A., Balasubramanian GP., Blattner-Johnson M., Worst BC., Stark S., Witt H., Pajtler KW., van Tilburg CM., Witt R., Milde T., Jakobs M., Fiesel P., Frühwald MC., Hernáiz Driever P., Thomale UW., Schuhmann MU., Metzler M., Bochennek K., Simon T., Dürken M., Karremann M., Knirsch S., Ebinger M., von Bueren AO., Pietsch T., Herold-Mende C., Reuss DE., Kling K., Lichter P., Eggert A., Kramm CM., Pfister SM., Jones DTW., Bächli H., Witt O.

Data di Pubblicazione: 2019-4-26

Abstract: In this multicentre study setting, brainstem biopsy of DIPG was feasible and yielded sufficient material for comprehensive molecular profiling. Relevant molecular targets were identified impacting clinical management in a substantial subset. Death or severe bleeding occurred in none of the cases. One of 20 patients experienced unilateral paraesthesia possibly related to biopsy.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 31005212

DOI: doi.org/10.1016/j.radonc.2019.01.008

Titolo: Low perfusion compartments in glioblastoma quantified by advanced magnetic resonance imaging and correlated with patient survival.

Autori: Li C., Yan JL., Torheim T., McLean MA., Boonzaier NR., Zou J., Huang Y., Yuan J., van Dijken BRJ., Matys T., Markowitz F., Price SJ.

Data di Pubblicazione: 2019-4-22

Abstract: Our results suggest that the ADC

Journal Title: Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology

PUBMED ID: 30977058

DOI: doi.org/10.1007/s11060-019-03166-3

Titolo: Dose-intensified chemoradiation is associated with altered patterns of failure and favorable survival in patients with newly diagnosed glioblastoma.

Autori: Kim MM., Speers C., Li P., Schipper M., Junck L., Leung D., Orringer D., Heth J., Umemura Y., Spratt DE., Wahl DR., Cao Y., Lawrence TS., Tsien C I.

Data di Pubblicazione: 2019-4-13

Abstract: Dose-escalated chemoRT resulted in lower rates of central recurrence and prolonged time to progression compared to historical controls, although a significant number of central recurrences were still observed. Advanced imaging and correlative molecular studies may enable targeted treatment advances that reduce rates of in- and out-of-field progression.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30974347

DOI: doi.org/10.1016/j.yebeh.2018.10.038

Titolo: Seizure characteristics, treatment, and outcome in autoimmune synaptic encephalitis: A long-term study.

Autori: Zhang W., Wang X., Shao N., Ma R., Meng H.

Data di Pubblicazione: 2019-4-12

Abstract: A complex of clinical and subclinical seizures, and nonepileptic events characterize ASE. Patients with anti-LGI1 or anti-GABA

Journal Title: Epilepsy & behavior : E&B

PUBMED ID: 30949360

DOI: doi.org/10.1093/nop/npy023

Titolo: Neurosurgical patterns of care for diffuse low-grade gliomas in Sweden between 2005 and 2015.

Autori: Carstam L., Smits A., Milos P., Corell A., Henriksson R., Bartek J., Jakola AS.

Data di Pubblicazione: 2019-4-6

Abstract: In this nationwide, population-based study we observed a shift over time in favor of LGG resection. Further, a positive correlation between the more active surgical strategy and longer survival is shown, although no causality can be claimed because of possible confounding factors.

Journal Title: Neuro-oncology practice

PUBMED ID: 30937703

DOI: doi.org/10.1007/s10014-019-00339-w

Titolo: Overview of DNA methylation in adult diffuse gliomas.

Autori: Aoki K., Natsume A.

Data di Pubblicazione: 2019-4-3

Abstract: Adult diffuse gliomas form a heterogeneous group of tumors of the central nervous system that vary greatly in histology and prognosis. A significant advance during the last decade has been the identification of a set of genetic lesions that correlate well with histology and clinical outcome in diffuse gliomas. Most characteristic driver mutations consist of isocitrate dehydrogenase 1 (IDH1) and IDH2, and H3 histone family member 3A, which are strongly associated with DNA and histone methylation patterns. A well-characterized DNA methylation aberration is on the O6-methylguanine-DNA methyltransferase promoter. This aberration is associated with an improved response to the DNA alkylating agent, temozolomide. Methylation alterations are used for classification or treatment decisions of diffuse gliomas. This supports the importance of considering epigenomic aberrations in the pathogenesis of gliomas. Recent DNA methylation analyses revealed a small group of IDH mutant diffuse gliomas exhibiting decreased DNA hypermethylation resulting in substantial unfavorable prognosis comparable to glioblastoma. Thus, DNA methylation patterns may become a new standard that replaces the conventional grading system based on histological diagnosis. In this review, we summarize recent developments regarding the contributions of methylation patterns to the pathogenesis of adult diffuse glioma, the interactions between methylation patterns and driver mutations, and potential epigenomic targeted therapies.

Journal Title: Brain tumor pathology

PUBMED ID: 30912721

DOI: doi.org/10.1148/radiol.2019182095

Titolo: Cost-effectiveness of Intraoperative MRI for Treatment of High-Grade Gliomas.

Autori: Abraham P., Sarkar R., Brandel MG., Wali AR., Rennert RC., Lopez Ramos C., Padwal J., Steinberg JA., Santiago-Dieppa DR., Cheung V., Pannell JS., Murphy JD., Khalessi AA.

Data di Pubblicazione: 2019-3-27

**Abstract:** Background Intraoperative MRI has been shown to improve gross-total resection of high-grade glioma. However, to the knowledge of the authors, the cost-effectiveness of intraoperative MRI has not been established. Purpose To construct a clinical decision analysis model for assessing intraoperative MRI in the treatment of high-grade glioma. Materials and Methods An integrated five-state microsimulation model was constructed to follow patients with high-grade glioma. One-hundred-thousand patients treated with intraoperative MRI were compared with 100 000 patients who were treated without intraoperative MRI from initial resection and debulking until death (median age at initial resection, 55 years). After the operation and treatment of complications, patients existed in one of three health states: progression-free survival (PFS), progressive disease, or dead. Patients with recurrence were offered up to two repeated resections. PFS, valuation of health states (utility values), probabilities, and costs were obtained from randomized controlled trials whenever possible. Otherwise, national databases, registries, and nonrandomized trials were used. Uncertainty in model inputs was assessed by using deterministic and probabilistic sensitivity analyses. A health care perspective was used for this analysis. A willingness-to-pay threshold of \$100 000 per quality-adjusted life year (QALY) gained was used to determine cost efficacy. Results Intraoperative MRI yielded an incremental benefit of 0.18 QALYs (1.34 QALYs with intraoperative MRI vs 1.16 QALYs without) at an incremental cost of \$13 447 (\$176 460 with intraoperative MRI vs \$163 013 without) in microsimulation modeling, resulting in an incremental cost-effectiveness ratio of \$76 442 per QALY. Because of parameter distributions, probabilistic sensitivity analysis demonstrated that intraoperative MRI had a 99.5% chance of cost-effectiveness at a willingness-to-pay threshold of \$100 000 per QALY. Conclusion Intraoperative MRI is likely to be a cost-effective modality in the treatment of high-grade glioma. © RSNA, 2019

Journal Title: Radiology

PUBMED ID: 30903281

DOI: doi.org/10.1007/s00381-019-04117-z

Titolo: Bevacizumab-containing regimen in relapsed/progressed brain tumors: a single-institution experience.

Autori: Schiavetti A., Varrasso G., Mollace MG., Dominici C., Ferrara E., Pappoff P., Di Biasi C.

Data di Pubblicazione: 2019-3-24

**Abstract:** BVZ/IRI association ± TMZ showed encouraging therapeutic activity and low toxicity in this series of relapsed/refractory brain tumors.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 30899304

DOI: doi.org/10.5114/aoms.2017.69374

Titolo: MiR-21, miR-34a, miR-125b, miR-181d and miR-648 levels inversely correlate with MGMT and TP53 expression in primary glioblastoma patients.

Autori: Jesionek-Kupnicka D., Braun M., Trąbska-Kluch B., Czech J., Szybka M., Szymańska B., Kulczycka-Wojdala D., Bieńkowski M., Kordek R., Zawlik I.

Data di Pubblicazione: 2019-3-23

**Abstract:** Our findings demonstrate that selected miRNAs are significantly correlated with

Journal Title: Archives of medical science : AMS

PUBMED ID: 30867563

DOI: doi.org/10.1038/s41416-019-0413-x

Titolo: High filamin-C expression predicts enhanced invasiveness and poor outcome in glioblastoma multiforme.

Autori: Kamil M., Shinsato Y., Higa N., Hirano T., Idogawa M., Takajo T., Minami K., Shimokawa M., Yamamoto M., Kawahara K., Yonezawa H., Hirano H., Furukawa T., Yoshimoto K., Arita K.

Data di Pubblicazione: 2019-3-15

Abstract: FLNC is a potential therapeutic target and biomarker for GBM progression.

Journal Title: British journal of cancer

PUBMED ID: 30857221

DOI: doi.org/10.3390/cancers11030336

Titolo: Glioblastoma in Elderly Patients: Current Management and Future Perspectives.

Autori: Minniti G., Lombardi G., Paolini S.

Data di Pubblicazione: 2019-3-13

Abstract: The incidence of glioblastoma (GBM) in the elderly population is slowly increasing in Western countries. Current management includes surgery, radiation therapy (RT) and chemotherapy; however, survival is significantly worse than that observed in younger patients and the optimal treatment in terms of efficacy and safety remains a matter of debate. Surgical resection is often employed as initial treatment for elderly patients with GBM, although the survival benefit is modest. Better survival has been reported in elderly patients treated with RT compared with those receiving supportive care alone, with similar survival outcome for patients undergoing standard RT (60 Gy over 6 weeks) and hypofractionated RT (25-40 Gy in 5-15 daily fractions). Temozolomide, an alkylating agent, may represent an effective and safe therapy in patients with promoter methylation of O<sup>6</sup>-methylguanine-DNA-methyltransferase (

Journal Title: Cancers

PUBMED ID: 30854437

DOI: doi.org/10.18383/j.tom.2018.00049

Titolo: Comparison of Voxel-Wise and Histogram Analyses of Glioma ADC Maps for Prediction of Early Therapeutic Change.

Autori: Chenevert TL., Malyarenko DI., Galbán CJ., Gomez-Hassan DM., Sundgren PC., Tsien CI., Ross BD.

Data di Pubblicazione: 2019-3-12

Abstract: Noninvasive imaging methods are sought to objectively predict early response to therapy for high-grade glioma tumors. Quantitative metrics derived from diffusion-weighted imaging, such as apparent diffusion coefficient (ADC), have previously shown promise when used in combination with voxel-based analysis reflecting regional changes. The functional diffusion mapping (fDM) metric is hypothesized to be associated with volume of tumor exhibiting an increasing ADC owing to effective therapeutic action. In this work, the reference fDM-predicted survival (from previous study) for 3 weeks from treatment initiation (midtreatment) is compared to multiple histogram-based metrics using Kaplan-Meier estimator for 80 glioma patients stratified to responders and nonresponders based on the population median value for the given metric. The ADC histogram metric reflecting reduction in midtreatment volume of solid tumor ( $ADC < 1.25 \times 10$

Journal Title: Tomography (Ann Arbor, Mich.)

PUBMED ID: 30835699

DOI: doi.org/10.3171/2018.10.PEDS18377

Titolo: Childhood brain tumors: current management, biological insights, and future directions.

Autori: Pollack IF., Agnihotri S., Broniscer A.



Data di Pubblicazione: 2019-3-6

Abstract: Brain tumors are the most common solid tumors in children, and, unfortunately, many subtypes continue to have a suboptimal long-term outcome. During the last several years, however, remarkable advances in our understanding of the molecular underpinnings of these tumors have occurred as a result of high-resolution genomic, epigenetic, and transcriptomic profiling, which have provided insights for improved tumor categorization and molecularly directed therapies. While tumors such as medulloblastomas have been historically grouped into standard- and high-risk categories, it is now recognized that these tumors encompass four or more molecular subsets with distinct clinical and molecular characteristics. Likewise, high-grade glioma, which for decades was considered a single high-risk entity, is now known to comprise multiple subsets of tumors that differ in terms of patient age, tumor location, and prognosis. The situation is even more complex for ependymoma, for which at least nine subsets of tumors have been described. Conversely, the majority of pilocytic astrocytomas appear to result from genetic changes that alter a single, therapeutically targetable molecular pathway. Accordingly, the present era is one in which treatment is evolving from the historical standard of radiation and conventional chemotherapy to a more nuanced approach in which these modalities are applied in a risk-adapted framework and molecularly targeted therapies are implemented to augment or, in some cases, replace conventional therapy. Herein, the authors review advances in the categorization and treatment of several of the more common pediatric brain tumors and discuss current and future directions in tumor management that hold significant promise for patients with these challenging tumors.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 30832617

DOI: doi.org/10.1186/s12885-019-5413-y

Titolo: Phase I/IIa study of concomitant radiotherapy with olaparib and temozolomide in unresectable or partially resectable glioblastoma: OLA-TMZ-RTE-01 trial protocol.

Autori: Lesueur P., Lequesne J., Grellard JM., Dugué A., Coquan E., Brachet PE., Geffrelet J., Kao W., Emery E., Berro DH., Castera L., Goardon N., Lacroix J., Lange M., Capel A., Leconte A., Andre B., Léger A., Lelaidier A., Clarisse B., Stefan D.

Data di Pubblicazione: 2019-3-6

Abstract: NCT03212742 , registered June, 7, 2017. Protocol version: Version 2.2 dated from 2017/08/18.

Journal Title: BMC cancer

PUBMED ID: 30830679

DOI: doi.org/10.1007/s11060-019-03140-z

Titolo: Nimotuzumab and radiotherapy for treatment of newly diagnosed diffuse intrinsic pontine glioma (DIPG): a phase III clinical study.

Autori: Fleischhack G., Massimino M., Warmuth-Metz M., Khuhlaeva E., Janssen G., Graf N., Rutkowski S., Beilken A., Schmid I., Biassoni V., Gorelishev SK., Kramm C., Reinhard H., Schlegel PG., Kortmann RD., Reuter D., Bach F., Izaguirre-Navarro NE., Bode U.

Data di Pubblicazione: 2019-3-5

Abstract: Concomitant treatment with RT and nimotuzumab was feasible in an outpatient setting. The PFS and OS were comparable to results achieved with RT and intensive chemotherapy in hospitalized setting.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30820715

DOI: doi.org/10.1007/s00432-019-02868-5

Titolo: Regorafenib in patients with recurrent high-grade astrocytoma.  
Autori: Kebir S., Rauschenbach L., Radbruch A., Lazaridis L., Schmidt T., Stoppel AK., Pierscianek D., Stuschke M., Forsting M., Sure U., Keyvani K., Kleinschnitz C., Scheffler B., Glas M.  
Data di Pubblicazione: 2019-3-2  
Abstract: This retrospective study indicates a very poor performance of regorafenib in recurrent high-grade astrocytoma with a fairly high number of CTC<sup>°3</sup> adverse events. In addition, regorafenib does not seem to bear a potential for infiltrative tumor growth promotion.  
Journal Title: Journal of cancer research and clinical oncology

PUBMED ID: 30810873  
DOI: doi.org/10.1007/s11060-019-03133-y  
Titolo: Quantifying radiation therapy response using apparent diffusion coefficient (ADC) parametric mapping of pediatric diffuse intrinsic pontine glioma: a report from the pediatric brain tumor consortium.  
Autori: Ceschin R., Kocak M., Vajapeyam S., Pollack IF., Onar-Thomas A., Dunkel IJ., Poussaint TY., Panigrahy A.  
Data di Pubblicazione: 2019-2-28  
Abstract: Baseline ADC values are a stronger predictor of outcome compared to radiation related ADC changes in pediatric DIPG. We show the feasibility of employing parametric mapping techniques in multi-center studies to quantify spatially heterogeneous treatment response in pediatric tumors, including DIPG.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 30806888  
DOI: doi.org/10.1007/s11060-019-03132-z  
Titolo: pH-weighted amine chemical exchange saturation transfer echoplanar imaging (CEST-EPI) as a potential early biomarker for bevacizumab failure in recurrent glioblastoma.  
Autori: Yao J., Tan CHP., Schlossman J., Chakhoyan A., Raymond C., Pope WB., Salamon N., Lai A., Ji M., Nghiemphu PL., Liau LM., Cloughesy TF., Ellingson BM.  
Data di Pubblicazione: 2019-2-27  
Abstract: This pilot study suggests pH-weighted amine CEST MRI may have value as a non-invasive, early imaging biomarker for bevacizumab treatment response and failure. Early decreases MTR  
Journal Title: Journal of neuro-oncology

PUBMED ID: 30771200  
DOI: doi.org/10.1007/s11060-019-03125-y  
Titolo: A multicenter phase II study of temozolomide plus disulfiram and copaxone for recurrent temozolomide-resistant glioblastoma.  
Autori: Huang J., Chaudhary R., Cohen AL., Fink K., Goldlust S., Boockvar J., Chinnaiyan P., Wan L., Marcus S., Campian JL.  
Data di Pubblicazione: 2019-2-17  
Abstract: Addition of DSF/Cu to TMZ for TMZ-resistant IDH-wild type GBM appears well tolerated but has limited activity for unselected population.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 30768441  
DOI: doi.org/10.1097/COC.0000000000000519  
Titolo: Concurrent Versus Sequential Chemoradiation for Low-grade Gliomas Meeting RTOG 9802 Criteria.  
Autori: Ryckman JM., Appiah AK., Lyden E., Verma V., Zhang C.

Data di Pubblicazione: 2019-2-16

Abstract: This is the only analysis of which we are aware of cCRT versus sCRT for LGG. There is no evidence that cCRT improves outcomes over sCRT.

Journal Title: American journal of clinical oncology

PUBMED ID: 30740109

DOI: doi.org/10.3389/fimmu.2018.03062

Titolo: Genetically Engineered T-Cells for Malignant Glioma: Overcoming the Barriers to Effective Immunotherapy.

Autori: Chuntova P., Downey KM., Hegde B., Almeida ND., Okada H.

Data di Pubblicazione: 2019-2-12

Abstract: Malignant gliomas carry a dismal prognosis. Conventional treatment using chemo- and radiotherapy has limited efficacy with adverse events. Therapy with genetically engineered T-cells, such as chimeric antigen receptor (CAR) T-cells, may represent a promising approach to improve patient outcomes owing to their potential ability to attack highly infiltrative tumors in a tumor-specific manner and possible persistence of the adaptive immune response. However, the unique anatomical features of the brain and susceptibility of this organ to irreversible tissue damage have made immunotherapy especially challenging in the setting of glioma. With safety concerns in mind, multiple teams have initiated clinical trials using CAR T-cells in glioma patients. The valuable lessons learnt from those trials highlight critical areas for further improvement: tackling the issues of the antigen presentation and T-cell homing in the brain, immunosuppression in the glioma microenvironment, antigen heterogeneity and off-tumor toxicity, and the adaptation of existing clinical therapies to reflect the intricacies of immune response in the brain. This review summarizes the up-to-date clinical outcomes of CAR T-cell clinical trials in glioma patients and examines the most pressing hurdles limiting the efficacy of these therapies. Furthermore, this review uses these hurdles as a framework upon which to evaluate cutting-edge pre-clinical strategies aiming to overcome those barriers.

Journal Title: Frontiers in immunology

PUBMED ID: 30737615

DOI: doi.org/10.1208/s12248-019-0302-5

Titolo: Estimation of Solid Tumor Doubling Times from Progression-Free Survival Plots Using a Novel Statistical Approach.

Autori: Kay K., Dolcy K., Bies R., Shah DK.

Data di Pubblicazione: 2019-2-10

Abstract: Tumor doubling time can significantly affect the outcome of anticancer therapy, but it is very challenging to determine. Here, we present a statistical approach that extracts doubling times from progression-free survival (PFS) plots, which inherently contains information regarding the growth of solid tumors. Twelve cancers were investigated and multiple PFS plots were evaluated for each type. The PFS plot showing fastest tumor growth was deemed to best represent the inherent growth kinetics of the solid tumor, and selected for further analysis. The exponential tumor growth rates were extracted from each PFS plot, along with associated variabilities, which ultimately allowed for the estimation of solid tumor doubling times. The mean simulated doubling times for pancreatic cancer, melanoma, hepatocellular carcinoma (HCC), renal cell carcinoma, triple negative breast cancer, non-small cell lung cancer, hormone receptor positive (HR+) breast cancer, human epidermal growth factor receptor-2 positive (HER-2+) breast cancer, gastric cancer, glioblastoma multiforme, colorectal cancer, and prostate cancer were 5.06, 3.78, 3.06, 2.67, 2.38, 2.40, 4.31, 4.12, and 3.84 months, respectively. For all cancers, clinically reported doubling times were within the estimated ranges. For all cancers, except HCC, the growth rates were best characterized by a log-normal distribution. For HCC, the gamma distribution best described the data.

ta. The statistical approach presented here provides a qualified method for extracting tumor growth rates and doubling times from PFS plots. It also allows estimation of the distributional characteristics for tumor growth rates and doubling times in a given patient population.  
Journal Title: The AAPS journal

PUBMED ID: 30737018

DOI: doi.org/10.1016/j.bulcan.2019.01.008

Titolo: [MSI Metastatic solid tumors treatment and immunotherapies].

Autori: Bouchez C., Kempf E., Tournigand C.

Data di Pubblicazione: 2019-2-10

Abstract: Checkpoint inhibitors are known to induce striking tumor responses in advanced MSI colorectal cancers, which used to be related to a poor clinical outcome. The incidence of the MSI phenotype is highly heterogeneous across non-colorectal cancers. The highest incidence rates are found in endometrioid forms of uterine cancers and in gastric tumors (20 to 40 % and 10 to 33 %, respectively). The association between a "MSI" tumor phenotype and other clinical or biological tumor characteristics is still under debate. Its prognostic value has not been determined yet. The deficiency of the DNA mismatch repair (dMMR) system of such tumor cells increases their mutational load and induces the production of so-called neo-antigens. Therefore, checkpoint inhibitors are a target therapeutic class for this molecular group of tumors. For example, response rates reach more than 50 % in pre-treated advanced endometrial cancers and in metastatic gastric tumors in association with a first line of chemotherapy. Those promising results imply the development of reliable biomarkers predictive of tumor response to immunotherapy. The present article summarizes the clinical outcomes related to the administration of checkpoint inhibitors in non-colorectal cancers. The ongoing clinical trials of such therapeutic class in this patient population are displayed.

Journal Title: Bulletin du cancer

PUBMED ID: 30713832

DOI: doi.org/10.3389/fonc.2018.00643

Titolo: Case Report: Clinical Outcome and Image Response of Two Patients With Secondary High-Grade Glioma Treated With Chemoradiation, PCV, and Cannabidiol.

Autori: Dall'Stella PB., Docema MFL., Maldaun MVC., Feher O., Lancellotti CLP.

Data di Pubblicazione: 2019-2-5

Abstract: We describe two patients with a confirmed diagnosis of high-grade gliomas (grades III/IV), both presenting with O6-methylguanine-DNA methyltransferase (MGMT) methylated and isocitrate dehydrogenase (IDH-1) mutated who, after subtotal resection, were submitted to chemoradiation and followed by PCV, a multiple drug regimen (procarbazine, lomustine, and vincristine) associated with cannabidiol (CBD). Both patients presented with satisfactory clinical and imaging responses at periodic evaluations. Immediately after chemoradiation therapy, one of the patients presented with an exacerbated and precocious pseudoprogression (PSD) assessed by magnetic resonance imaging (MRI), which was resolved in a short period. The other patient presented with a marked remission of altered areas compared with the post-operative scans as assessed by MRI. Such aspects are not commonly observed in patients only treated with conventional modalities. This observation might highlight the potential effect of CBD to increase PSD or improve chemoradiation responses that impact survival. Further investigation with more patients and critical molecular analyses should be performed.

Journal Title: Frontiers in oncology

PUBMED ID: 30705664

DOI: doi.org/10.3389/fneur.2018.01199

Titolo: ZEB1 Is a Transcription Factor That Is Prognostic and Predictive in Diffuse Gliomas.

Autori: Edwards LA., Kim S., Madany M., Nuno M., Thomas T., Li A., Berel D., Lee BS., Liu M., Black KL., Fan X., Zhang W., Yu JS.

Data di Pubblicazione: 2019-2-2

Abstract: None

Journal Title: Frontiers in neurology

PUBMED ID: 30680470

DOI: doi.org/10.1007/s10689-019-00121-z

Titolo: Mutated SON putatively causes a cancer syndrome comprising high-risk medulloblastoma combined with café-au-lait spots.

Autori: Chiu C., Loth S., Kuhlen M., Ginzler S., Schaper J., Rosenbaum T., Pietsch T., Borkhardt A., Hoell JI.

Data di Pubblicazione: 2019-1-26

Abstract: Medulloblastoma is the most frequent malignant brain tumor in childhood. This highly malignant neoplasm occurs usually before 10 years of age and more frequently in boys. The 5-year event-free survival rate for high-risk medulloblastoma is low at 62% despite a multimodal therapy including surgical resection, radiation therapy and chemotherapy. We report the case of a boy, who was born to consanguineous parents. Prominently, he had multiple café-au-lait spots. At the age of 3 years he was diagnosed with a high-risk metastatic medulloblastoma. The patient died only 11 months after diagnosis of a fulminant relapse presenting as meningeal and spinal dissemination. Whole-exome sequencing of germline DNA was employed to detect the underlying mutation for this putative cancer syndrome presenting with the combination of medulloblastoma and skin alterations. After screening all possible homozygous gene SNVs, we identified a mutation of SON, an essential protein in cell cycle regulation and cell proliferation, as the most likely genetic cause.

Journal Title: Familial cancer

PUBMED ID: 30668823

DOI: doi.org/10.1093/neuonc/noz016

Titolo: Accelerated progression of IDH mutant glioma after first recurrence.

Autori: Miller JJ., Loebel F., Juratli TA., Tummala SS., Williams EA., Batchelor TT., Arrillaga-Romany I., Cahill DP.

Data di Pubblicazione: 2019-1-23

Abstract: We report outcomes in a large cohort of IDH mutant glioma, providing a well-characterized historical control population for future clinical trial design. Notably, the interval between first and second recurrence (PFS2, 3.0 y) is shorter than time from diagnosis to first recurrence (PFS1, 5.7 y), evidence that these tumors clinically degenerate from an indolent course to an accelerated malignant phase. Thus, PFS2 represents a relevant outcome for trials investigating drug efficacy at recurrence.

Journal Title: Neuro-oncology

PUBMED ID: 30659522

DOI: doi.org/10.1007/s11060-019-03103-4

Titolo: 5-aminolevulinic acid photodynamic therapy for the treatment of high-grade gliomas.

Autori: Mahmoudi K., Garvey KL., Bouras A., Cramer G., Stepp H., Jesu Raj JG., Bozec D., Busch TM., Hadjipanayis CG.

Data di Pubblicazione: 2019-1-20

Abstract: PDT remains a promising therapeutic approach that requires further study in HGGs. Use of 5-ALA PDT permits selective tumor targeting due to the

intracellular metabolism of 5-ALA. The immunomodulatory effects of PDT further strengthen its use for treatment of HGGs and requires a better understanding. The combination of PDT with adjuvant therapies for HGGs will need to be studied in randomized, controlled studies.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 30639498  
DOI: doi.org/10.1016/j.wneu.2018.12.147  
Titolo: H3 K27M Mutations in Thalamic Pilocytic Astrocytomas with Anaplasia.  
Autori: El Ahmadi TY., Plitt A., Kafka B., Aoun SG., Raisanen JM., Orr B., Pan E., Wardak Z., Nedzi LA., Patel TR.  
Data di Pubblicazione: 2019-1-15  
Abstract: Stereotactic biopsies may undergrade some adult thalamic pilocytic astrocytomas. Thus, we recommend that all of these tumors be evaluated for the H3 K27M mutation. Further, we believe that H3 K27M-mutant thalamic pilocytic astrocytomas require aggressive multi-modality treatment and that these treatments should be guided by the molecular findings, as opposed to the histologic ones.  
Journal Title: World neurosurgery

PUBMED ID: 30635340  
DOI: doi.org/10.1158/1078-0432.CCR-18-3101  
Titolo: The Misclassification of Diffuse Gliomas: Rates and Outcomes.  
Autori: Iorgulescu JB., Torre M., Harary M., Smith TR., Aizer AA., Reardon D A., Barnholtz-Sloan JS., Perry A.  
Data di Pubblicazione: 2019-1-13  
Abstract: On the basis of 1p/19q, IDH, ATRX, and p53, the misclassification rates of histologically encoded oligodendrogliomas, astrocytomas, and glioblastomas are approximately 21%-35%, 6%-9%, and 9%, respectively; with significant clinical implications. Our findings suggest that when compared with historical histology-only classified data, in national registry, as well as, in institutional databases, there is the potential for false-positive results in contemporary trials of molecularly classified diffuse gliomas, which could contribute to a seemingly positive phase II trial (based on historical comparison) failing at the phase III stage. Critically, findings from diffuse glioma clinical trials and historical cohorts using prior histology-only WHO schemes must be cautiously reinterpreted.  
Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 30610982  
DOI: doi.org/10.1016/j.wneu.2018.12.118  
Titolo: The Role and Real Effect of an Iterative Surgical Approach for the Management of Recurrent High-Grade Glioma: An Observational Analytic Cohort Study.  
Autori: Salvati M., Pesce A., Palmieri M., Floriana Brunetto GM., Santoro A., Frati A.  
Data di Pubblicazione: 2019-1-6  
Abstract: These data showed excellent outcomes in terms of OS and PFS and clinical conditions after multiple surgical procedures. Therefore, reintervention appears to be a feasible and safe solution for selected patients.  
Journal Title: World neurosurgery

PUBMED ID: 30610915  
DOI: doi.org/10.1016/j.ijrobp.2018.12.043

Titolo: A Phase 1/2 Trial of Reirradiation for Diffuse Intrinsic Pontine Glioma.

Autori: Amsbaugh MJ., Mahajan A., Thall PF., McAleer MF., Paulino AC., Grosshans D., Khatua S., Ketonen L., Fontanilla H., McGovern SL.

Data di Pubblicazione: 2019-1-6

Abstract: ReRT can safely be delivered for progressive diffuse intrinsic pontine glioma. Clinical improvement was seen in almost all patients. Utility analysis suggests that a regimen of 24 Gy in 12 fractions is preferred.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 30602457

DOI: doi.org/10.1073/pnas.1721434116

Titolo: Microglia are effector cells of CD47-SIRP $\alpha$  antiphagocytic axis disruption against glioblastoma.

Autori: Hutter G., Theruvath J., Graef CM., Zhang M., Schoen MK., Manz EM., Bennett ML., Olson A., Azad TD., Sinha R., Chan C., Assad Kahn S., Gholamin S., Wilson C., Grant G., He J., Weissman IL., Mitra SS., Cheshier SH.

Data di Pubblicazione: 2019-1-4

Abstract: Glioblastoma multiforme (GBM) is a highly aggressive malignant brain tumor with fatal outcome. Tumor-associated macrophages and microglia (TAMs) have been found to be major tumor-promoting immune cells in the tumor microenvironment. Hence, modulation and reeducation of tumor-associated macrophages and microglia in GBM is considered a promising antitumor strategy. Resident microglia and invading macrophages have been shown to have distinct origin and function. Whereas yolk sac-derived microglia reside in the brain, blood-derived monocytes invade the central nervous system only under pathological conditions like tumor formation. We recently showed that disruption of the SIRP $\alpha$ -CD47 signaling axis is efficacious against various brain tumors including GBM primarily by inducing tumor phagocytosis. However, most effects are attributed to macrophages recruited from the periphery but the role of the brain resident microglia is unknown. Here, we sought to utilize a model to distinguish resident microglia and peripheral macrophages within the GBM-TAM pool, using orthotopically xenografted, immunodeficient, and syngeneic mouse models with genetically color-coded macrophages (

Journal Title: Proceedings of the National Academy of Sciences of the United States of America

PUBMED ID: 30569607

DOI: doi.org/10.1002/cam4.1799

Titolo: Use of bevacizumab as a single agent or in adjunct with traditional chemotherapy regimens in children with unresectable or progressive low-grade glioma.

Autori: Zhukova N., Rajagopal R., Lam A., Coleman L., Shipman P., Walwyn T., Williams M., Sullivan M., Campbell M., Bhatia K., Gottardo NG., Hansford JR.

Data di Pubblicazione: 2018-12-21

Abstract: In pediatric low-grade gliomas not amenable to complete resection, various chemotherapy regimens are the mainstream of treatment. An excellent overall survival of these patients makes justification of the intensification of chemotherapy difficult and calls for the development of new strategies. Bevacizumab, a humanized monoclonal antibody directed against Vascular endothelial growth factor (VEGF), has been successfully used in combination with irinotecan in a number of adult and pediatric studies and reports. Fifteen patients at median age of 7 years old (range 3 months to 15 years) were treated with bevacizumab in combination with conventional low-toxicity chemotherapy. The majority had chiasmatic/hypothalamic and midline tumors, seven had confirmed BRAF pathway alterations including neurofibromatosis type 1 (2). Fourteen patients had more than one progression and three had radiotherapy. No deaths were documented, PFS at 11 and 15 months was 71.5%  $\pm$  13.9% and 44.7

%  $\pm$  17.6% respectively. At the end of follow-up 40% of patients has radiologically stable disease, three patients progressed shortly after completion of bevacizumab and two showed mixed response with progression of cystic component. Rapid visual improvement was seen in 6/8 patients, resolution of endocrine symptoms in 2/4 and motor function improvement in 4/6. No relation between histology or BRAF status and treatment response was observed. Treatment-limiting toxicities included grade 4 proteinuria (2) and hypertension (2) managed with cessation (1) and pausing of therapy plus antihypertensives (1). In conclusion, bevacizumab is well tolerated and appears most effective for rapid tumor control to preserve vision and improve morbidity.

Journal Title: Cancer medicine

PUBMED ID: 30563210

DOI: doi.org/10.3390/ijms19123905

Titolo: Intranasal Perillyl Alcohol for Glioma Therapy: Molecular Mechanisms and Clinical Development.

Autori: Chen TC., da Fonseca CO., Schönthal AH.

Data di Pubblicazione: 2018-12-20

Abstract: Intracranial malignancies, such as primary brain cancers and brain-localized metastases derived from peripheral cancers, are particularly difficult to treat with therapeutic agents, because the blood-brain barrier (BBB) effectively minimizes brain entry of the vast majority of agents arriving from the systemic circulation. Intranasal administration of cancer drugs has the potential to reach the brain via direct nose-to-brain transport, thereby circumventing the obstacle posed by the BBB. However, in the field of cancer therapy, there is a paucity of studies reporting positive results with this type of approach. A remarkable exception is the natural compound perillyl alcohol (POH). Its potent anticancer activity was convincingly established in preclinical studies, but it nonetheless failed in subsequent clinical trials, where it was given orally and displayed hard-to-tolerate gastrointestinal side effects. Intriguingly, when switched to intranasal delivery, POH yielded highly promising activity in recurrent glioma patients and was well tolerated. As of 2018, POH is the only intranasally delivered compound in the field of cancer therapy (outside of cancer pain) that has advanced to active clinical trials. In the following, we will introduce this compound, summarize its molecular mechanisms of action, and present the latest data on its clinical evaluation as an intranasally administered agent for glioma.

Journal Title: International journal of molecular sciences

PUBMED ID: 30561851

DOI: doi.org/10.1002/cam4.1908

Titolo: Combining multimodal imaging and treatment features improves machine learning-based prognostic assessment in patients with glioblastoma multiforme.

Autori: Peeken JC., Goldberg T., Pyka T., Bernhofer M., Wiestler B., Kessel KA., Tafti PD., Nüsslin F., Braun AE., Zimmer C., Rost B., Combs SE.

Data di Pubblicazione: 2018-12-19

Abstract: MRI-based features were the most relevant feature class for prognostic assessment. Combining clinical, pathological, and imaging information increased predictive power for OS and PFS. A further increase was achieved by adding treatment features.

Journal Title: Cancer medicine

PUBMED ID: 30554263

DOI: doi.org/10.1007/s00381-018-4015-3

Titolo: Neurocognitive, academic and functional outcomes in survivors of infant ependymoma (UKCCSG CNS 9204).



Autori: Morrall MCHJ., Reed-Berendt R., Moss K., Stocks H., Houston AL., Siddell P., Picton S., Grundy R.

Data di Pubblicazione: 2018-12-17

Abstract: The relapsed irradiated ependymoma group demonstrated the most significantly impaired neurocognitive outcomes at long-term follow-up. Non-relapsing participants demonstrated better outcomes than those who relapsed. Results tentatively suggest avoiding radiotherapy helped preserve neurocognitive and learning outcomes of individuals diagnosed with ependymoma when aged  $\leq$  36 months old. Prospective neurocognitive surveillance is required. Recommendations for clinical and research practice are provided.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 30544336

DOI: doi.org/10.3171/2018.7.JNS18422

Titolo: Role of photodynamic therapy using talaporfin sodium and a semiconductor laser in patients with newly diagnosed glioblastoma.

Autori: Nitta M., Muragaki Y., Maruyama T., Iseki H., Komori T., Ikuta S., Saito T., Yasuda T., Hosono J., Okamoto S., Koriyama S., Kawamata T.

Data di Pubblicazione: 2018-12-15

Abstract: The results of the present study suggest that PDT with talaporfin sodium and a semiconductor laser provides excellent local control, with few adverse effects even in cases of multiple laser irradiations, as well as potential survival benefits for patients with newly diagnosed glioblastoma.

Journal Title: Journal of neurosurgery

PUBMED ID: 30523606

DOI: doi.org/10.1007/s11060-018-03065-z

Titolo: Association of patterns of care, prognostic factors, and use of radiotherapy-temozolomide therapy with survival in patients with newly diagnosed glioblastoma: a French national population-based study.

Autori: Fabbro-Peray P., Zouaoui S., Darlix A., Fabbro M., Pallud J., Rigau V., Mathieu-Daude H., Bessaoud F., Bauchet F., Riondel A., Sorbets E., Charissoux M., Amelot A., Mandonnet E., Figarella-Branger D., Duffau H., Tretarre B., Taillandier L., Bauchet L.

Data di Pubblicazione: 2018-12-8

Abstract: In non-progressive patients, prolonging the adjuvant temozolomide beyond 6 cycles may improve OS.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30522967

DOI: doi.org/10.1016/S1470-2045(18)30675-2

Titolo: Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial.

Autori: Lombardi G., De Salvo GL., Brandes AA., Eoli M., Rudà R., Faedi M., Lolli I., Pace A., Daniele B., Pasqualetti F., Rizzato S., Bellu L., Pambuku A., Farina M., Magni G., Indraccolo S., Gardiman MP., Soffietti R., Zagonel V.

Data di Pubblicazione: 2018-12-8

Abstract: Veneto Institute of Oncology and Bayer Italy.

Journal Title: The Lancet. Oncology

PUBMED ID: 30535596

DOI: doi.org/10.1007/s11060-018-03075-x

Titolo: Baseline multicentric tumors, distant recurrences and leptomeningeal dissemination predict poor survival in patients with recurrent glioblastomas receiving bevacizumab.

Autori: Toh CH., Liao CT., Wei KC., Castillo M.

Data di Pubblicazione: 2018-12-12

Abstract: Baseline multicentric tumors, distant recurrence and leptomeningeal dissemination predicted poor survival among patients receiving bevacizumab for recurrent GB. Conventional MRI may help selecting patients with recurrent GB for bevacizumab treatment.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30515706

DOI: doi.org/10.1007/s11060-018-03059-x

Titolo: Re-irradiation for recurrent glioma: outcome evaluation, toxicity and prognostic factors assessment. A multicenter study of the Radiation Oncology Italian Association (AIRO).

Autori: Navarria P., Minniti G., Clerici E., Tomatis S., Pinzi V., Ciammella P., Galaverni M., Amelio D., Scartoni D., Scoccianti S., Krengli M., Masini L., Draghini L., Maranzano E., Borzillo V., Muto P., Ferrarese F., Fariselli L., Livi L., Pasqualetti F., Fiorentino A., Alongi F., di Monale MB., Magrin S., Scorsetti M.

Data di Pubblicazione: 2018-12-6

Abstract: our data underline re-RT as a safe and feasible treatment with limited rate of toxicity, and a combined ones as a better option for selected patients. The identification of a BED threshold able to obtain a greater benefit on OS, can help in designing future prospective studies.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30488830

DOI: doi.org/10.4103/jcrt.JCRT\_295\_17

Titolo: Impact of subventricular zone irradiation on outcome of patients with glioblastoma.

Autori: Mathew BS., Kaliyath SB., Krishnan J., Bhasi S.

Data di Pubblicazione: 2018-11-30

Abstract: This retrospective study indicated a trend toward improved-albeit nonsignificant-survival with higher dose to the ipsilateral and contralateral SVZs. A well-designed prospective randomized study is required to identify patients who would benefit from intentional SVZ targeting.

Journal Title: Journal of cancer research and therapeutics

PUBMED ID: 30488294

DOI: doi.org/10.1007/s11060-018-03063-1

Titolo: Increase of pseudoprogression and other treatment related effects in low-grade glioma patients treated with proton radiation and temozolomide.

Autori: Dworkin M., Mehan W., Niemierko A., Kamran SC., Lamba N., Dietrich J., Martinez-Lage M., Oh KS., Batchelor TT., Wen PY., Loeffler JS., Shih HA.

Data di Pubblicazione: 2018-11-30

Abstract: TMZ use, when added to PRT, was associated with increased PsP in patients with LGG; however, patients with PsP tended to achieve longer survival.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30485241

DOI: doi.org/10.3171/2018.7.SPINE18230

Titolo: Intramedullary spinal cord ependymoma and astrocytoma: intraoperative frozen-section diagnosis, extent of resection, and outcomes.

Autori: Hongo H., Takai K., Komori T., Taniguchi M.

Data di Pubblicazione: 2018-11-29

**Abstract:** **OBJECTIVE** The intraoperative differentiation of ependymomas from astrocytomas is important because neurosurgical strategies differ between these two tumor groups. Previous studies have reported that the diagnostic accuracy of intraoperative frozen sections of intracranial central nervous system (CNS) tumors is higher than 83%-97%, whereas that for spinal intramedullary tumors remains unknown. Herein, authors tested the hypothesis that intraoperative frozen-section diagnosis is the gold standard for a differential diagnosis of intramedullary spinal cord tumors. **METHODS** The clinical characteristics, intraoperative histological diagnosis from frozen sections, extent of tumor resection, progression-free survival (PFS), and overall survival (OS) of 49 cases of intramedullary spinal cord ependymomas (n = 32) and astrocytomas (n = 17) were retrospectively evaluated. **RESULTS** The frozen-section diagnosis and final diagnosis with permanent sections agreed in 23 (72%) of 32 cases of ependymoma. Of the 9 cases of ependymoma in which the frozen-section diagnosis disagreed with the final diagnosis, 4 were incorrectly diagnosed as astrocytoma and the other 5 cases had a nonspecific diagnosis, such as glioma. Nonetheless, gross-total resection was achieved in 6 of these 9 cases given the presence of a dissection plane. The frozen-section diagnosis and final diagnosis agreed in 12 (71%) of 17 cases of astrocytoma. Of the 5 cases of astrocytoma in which the frozen-section diagnosis disagreed with the final diagnosis, 1 was incorrectly diagnosed as ependymoma and the other 4 had a nonspecific diagnosis. Gross-total resection was achieved in only 1 of these 5 cases. A relationship between the size of tumor specimens and the diagnostic accuracy of frozen sections was not observed. Ependymal rosettes and perivascular pseudorosettes were observed in 30% and 57% of ependymomas, respectively, but were absent in astrocytomas. Progression-free survival and OS were both significantly longer in cases of ependymoma than in cases of astrocytoma (p < 0.001). Gross-total resection was achieved in 69% of ependymomas and was associated with longer PFS (p = 0.041). In the astrocytoma group, gross-total resection was achieved in only 12% and there was no relationship between extent of resection and OS. Tumor grades tended to correlate with OS in astrocytomas (p = 0.079). **CONCLUSIONS** The diagnostic accuracy of intraoperative frozen sections was lower for intramedullary spinal cord ependymomas and astrocytomas in the present study than that for intracranial CNS tumors reported on in the literature. Surgical strategies need to be selected based on multiple factors, such as clinical characteristics, preoperative imaging, frozen-section diagnosis, and intraoperative findings of the tumor plane.

Journal Title: Journal of neurosurgery. Spine

PUBMED ID: 30467813

DOI: doi.org/10.1007/s11060-018-03030-w

Titolo: Surgical management of lower-grade glioma in the spotlight of the 2016 WHO classification system.

Autori: Delev D., Heiland DH., Franco P., Reinacher P., Mader I., Staszewski O., Lassmann S., Grau S., Schnell O.

Data di Pubblicazione: 2018-11-24

**Abstract:** The impact of surgical treatment on the outcome of lower-grade gliomas depends to a great extent on the molecular subtype of the tumors. Patients with more aggressive tumors (IDH-wildtype) seem to profit from more intensive treatment like GTR, multiple resections and combined radio-/chemotherapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30464150

DOI: doi.org/10.2176/nmc.oa.2018-0111

Titolo: Boron Neutron Capture Therapy Combined with Early Successive Bevacizumab Treatments for Recurrent Malignant Gliomas - A Pilot Study.

Autori: Shiba H., Takeuchi K., Hiramatsu R., Furuse M., Nonoguchi N., Kawabata S., Kuroiwa T., Kondo N., Sakurai Y., Suzuki M., Ono K., Oue S., Ishikawa E., Michiue H., Miyatake SI.

Data di Pubblicazione: 2018-11-23

Abstract: Recurrent malignant gliomas (RMGs) are difficult to control, and no standard protocol has been established for their treatment. At our institute, we have often treated RMGs by tumor-selective particle radiation called boron neutron capture therapy (BNCT). However, despite the cell-selectivity of BNCT, brain radiation necrosis (BRN) may develop and cause severe neurological complications and sometimes death. This is partly due to the full-dose X-ray treatments usually given earlier in the treatment course. To overcome BRN following BNCT, recent studies have used bevacizumab (BV). We herein used extended BV treatment beginning just after BNCT to confer protection against or ameliorate BRN, and evaluated; the feasibility, efficacy, and BRN control of this combination treatment. Seven patients with RMGs (grade 3 and 4 cases) were treated with BNCT between June 2013 and May 2014, followed by successive BV treatments. They were followed-up to December 2017. Median overall survival (OS) and progression-free survival (PFS) after combination treatment were 15.1 and 5.4 months, respectively. In one case, uncontrollable brain edema occurred and ultimately led to death after BV was interrupted due to meningitis. In two other cases, symptomatic aggravation of BRN occurred after interruption of BV treatment. No BRN was observed during the observation period in the other cases. Common terminology criteria for adverse events grade 2 and 3 proteinuria occurred in two cases and necessitated the interruption of BV treatments. Boron neutron capture therapy followed by BV treatments well-prevented or well-controlled BRN with prolonged OS and acceptable incidence of adverse events in our patients with RMG.

Journal Title: Neurologia medico-chirurgica

PUBMED ID: 30460634

DOI: doi.org/10.1007/s11060-018-03055-1

Titolo: Infusion of 5-Azacytidine (5-AZA) into the fourth ventricle or resection cavity in children with recurrent posterior Fossa Ependymoma: a pilot clinical trial.

Autori: Sandberg DI., Yu B., Patel R., Hagan J., Miesner E., Sabin J., Smith S., Fletcher S., Shah MN., Sirianni RW., Taylor MD.

Data di Pubblicazione: 2018-11-22

Abstract: 5-AZA can be infused into the fourth ventricle or posterior fossa tumor resection cavity without causing neurological toxicity. Future studies with higher doses and/or increased dosing frequency are warranted.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30452715

DOI: doi.org/10.1093/neuonc/noy191

Titolo: Craniospinal irradiation as part of re-irradiation for children with recurrent intracranial ependymoma.

Autori: Tsang DS., Murray L., Ramaswamy V., Zapotocky M., Tabori U., Bartels U., Huang A., Dirks PB., Taylor MD., Hawkins C., Bouffet E., Laperriere N.

Data di Pubblicazione: 2018-11-20

Abstract: Re-irradiation with CSI is a safe and effective treatment for children with locally recurrent ependymoma and improves disease control compared with focal re-irradiation, with the benefit most apparent for those with infratentorial primary tumors.

Journal Title: Neuro-oncology

PUBMED ID: 30446361

DOI: doi.org/10.1016/j.jocn.2018.11.005

Titolo: Tumour volume reduction following PET guided intensity modulated radiation therapy and temozolomide in IDH mutated anaplastic glioma.

Autori: Back M., Jayamanne D., Brazier D., Bailey D., Hsiao E., Guo L., Wheeler H.

Data di Pubblicazione: 2018-11-18

Abstract: The role of maximal surgical debulking in isocitrate dehydrogenase (IDH) mutated anaplastic glioma prior to adjuvant radiation therapy remains uncertain. This study assessed the reduction in tumour volume following intensity modulated radiation therapy (IMRT) and temozolomide in this favourable and more responsive tumour pathology. 56 patients were managed from 2011 to 2014 and 53 had residual disease. To assess radiological response, tumour volumes were created on representative T1/T2Flair MRI sequences using identical slice-levels in three planes for pre-IMRT, month+3 and month+12 post-IMRT scans. Change in volumes was assessed between time periods. Progression-free survival (PFS) was calculated from start of radiotherapy. Median follow-up for survivors is 48.2 months. Pathology was anaplastic oligodendroglioma (AOD) and anaplastic astrocytoma IDH-mutated (AAMut) in 32 and 21 patients respectively. 93% received sequential chemotherapy. The median residual disease on T1 and T2Flair imaging was 9.7 cm

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 30419305

DOI: doi.org/10.1016/j.ijrobp.2018.11.004

Titolo: Conformal Radiation Therapy for Pediatric Patients with Low-Grade Glioma: Results from the Children's Oncology Group Phase 2 Study ACNS0221.

Autori: Cherlow JM., Shaw DWW., Margraf LR., Bowers DC., Huang J., Fouladi M., Onar-Thomas A., Zhou T., Pollack IF., Gajjar A., Kessel SK., Cullen PL., McMullen K., Wellons JC., Merchant TE.

Data di Pubblicazione: 2018-11-13

Abstract: For patients with PLGG, CRT with a CTV margin of 5 mm yields an acceptable PFS and does not lead to a high rate of marginal relapse.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 30417211

DOI: doi.org/10.1007/s00381-018-4001-9

Titolo: Nimotuzumab-containing regimen for pediatric diffuse intrinsic pontine gliomas: a retrospective multicenter study and review of the literature.

Autori: Kebudi R., Cakir FB., Bay SB., Gorgun O., Altınok P., Iribas A., Agoğlu FY., Darendeliler E.

Data di Pubblicazione: 2018-11-13

Abstract: Nimotuzumab-containing regimens are feasible and tolerable; it might be that some patients either with newly diagnosed DIPG or with progressive disease may benefit modestly from nimotuzumab-containing combinations.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 30396819

DOI: doi.org/10.1016/j.pan.2018.10.004

Titolo: Tumor treating fields in combination with gemcitabine or gemcitabine plus nab-paclitaxel in pancreatic cancer: Results of the PANOVA phase 2 study.

Autori: Rivera F., Benavides M., Gallego J., Guillen-Ponce C., Lopez-Martin J., Küng M.

Data di Pubblicazione: 2018-11-7

Abstract: The PANOVA trial demonstrated that the combination of TTFields and systemic chemotherapy is safe and tolerable in patients with advanced PDAC. Based on the safety and preliminary efficacy results of this phase 2 study, a randomized phase 3 study (PANOVA-3) is underway.

Journal Title: Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.]

PUBMED ID: 30392813

DOI: doi.org/10.1016/S1470-2045(18)30532-1

Titolo: Prognostic effect of whole chromosomal aberration signatures in standard-risk, non-WNT/non-SHH medulloblastoma: a retrospective, molecular analysis of the HIT-SIOP PNET 4 trial.

Autori: Goschzik T., Schwalbe EC., Hicks D., Smith A., Zur Muehlen A., Figarella-Branger D., Doz F., Rutkowski S., Lannering B., Pietsch T., Clifford SC .

Data di Pubblicazione: 2018-11-6

Abstract: Cancer Research UK, Swedish Childhood Cancer Foundation, French Ministry of Health/French National Cancer Institute, and the German Children's Cancer Foundation.

Journal Title: The Lancet. Oncology

PUBMED ID: 30392092

DOI: doi.org/10.1007/s11060-018-03003-z

Titolo: Pre-irradiation intensive induction and marrow-ablative consolidation chemotherapy in young children with newly diagnosed high-grade brainstem gliomas: report of the "head-start" I and II clinical trials.

Autori: Osorio DS., Patel N., Ji L., Spoto R., Stanek J., Gardner SL., Allen JC., Cornelius A., McCowage GB., Termuhlen A., Dunkel IJ., Comito M., Garvin J., Finlay JL.

Data di Pubblicazione: 2018-11-5

Abstract: Children with high-grade BSG did not benefit from this intensive chemotherapy strategy administered prior to irradiation.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30389317

DOI: doi.org/10.1016/j.prp.2018.10.023

Titolo: Cell division cycle associated 7 like predicts unfavorable prognosis and promotes invasion in glioma.

Autori: Shen FZ., Li XS., Ma JW., Wang XY., Zhao SP., Meng L., Liang SF., Zhao XL.

Data di Pubblicazione: 2018-11-4

Abstract: CDCA7L is highly expressed in human glioma tissues and a high CDCA7L expression level predicts the dismal prognosis for glioma patients. Moreover, CDCA7L can promote glioma invasion, which can serve as an independent potential prognostic biomarker for glioma patients.

Journal Title: Pathology, research and practice

PUBMED ID: 30366780

DOI: doi.org/10.1016/j.jocn.2018.10.084

Titolo: Glioneuronal brainstem tumor - It's all in the eyes.

Autori: Foster E., McLean C., White O.

Data di Pubblicazione: 2018-10-28

Abstract: A previously well man presented with several months' history of neurological symptoms including diplopia and balance difficulties. Examination revealed fluctuating neurological deficits, fatigable weakness and slowed sa

ccades. Extensive testing revealed mildly elevated cerebrospinal fluid protein, strongly positive single fiber electromyography and a dorsal pontine lesion at the floor of the 4th ventricle. An autoimmune process was felt to best account for the myasthenic presentation while the differential diagnoses for the brainstem lesion included glioma. Aggressive immunotherapy failed to halt clinical deterioration; over months he developed generalized weakness, aspiration pneumonia and died. Post-mortem analysis revealed glioneuronal tumor infiltration throughout the brainstem, cerebellum and along the meningeal surface. This is an unusual case of an infiltrative brainstem lesion, with the presentation suggesting a primary diagnosis of myasthenia gravis. The progressive nature of the illness, despite aggressive immune therapy, together with slow saccades, underscored a more sinister process. Cerebral imaging should be performed in patients with fluctuating neurological symptoms, progressive deterioration, and ocular, bulbar, respiratory, or pyramidal pattern deficits, and differentials for contrast-enhancing brain lesions should include primary brain tumors. In such cases, biopsy must proceed if the disease is of relatively recent onset, to facilitate diagnosis and maximize treatment opportunities.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 30361826

DOI: doi.org/10.1007/s13402-018-0411-7

Titolo: Molecular features unique to glioblastoma radiation resistant residual cells may affect patient outcome - a short report.

Autori: Kaur E., Goda JS., Ghorai A., Salunkhe S., Shetty P., Moiyadi AV., Sridhar E., Mahajan A., Jalali R., Dutt S.

Data di Pubblicazione: 2018-10-27

Abstract: Our data indicate that molecular features of innately radiation resistant GBM cells independently correlate with clinical outcome. Our study also highlights the relevance of using patient-derived primary GBM cultures for the characterization of RR cells that are otherwise inaccessible for analysis.

Journal Title: Cellular oncology (Dordrecht)

PUBMED ID: 30358225

DOI: Mancante

Titolo: Management and treatment of children with medulloblastoma in Serbia, a middle-income country.

Autori: Bokun J., Grujicic D., Skender-Gazibara M., Paripovic L., Pekmezovic T., Kusic-Tepavcevic D., Ilic V., Raicevic S., Stanic D., Miskovic I., Saric M., Nikitovic M.

Data di Pubblicazione: 2018-10-26

Abstract: In Serbia, a MIC, it is possible to achieve good treatment results in children with medulloblastoma using international treatment guidelines and recommendations, available resources and an experienced team of professionals dedicated to pediatric neurooncology.

Journal Title: Journal of B.U.ON. : official journal of the Balkan Union of Oncology

PUBMED ID: 30351999

DOI: doi.org/10.1200/JCO.2018.78.9990

Titolo: BRAF Inhibition in

Autori: Kaley T., Touat M., Subbiah V., Hollebecque A., Rodon J., Lockhart A C., Keedy V., Bielle F., Hofheinz RD., Joly F., Blay JY., Chau I., Puzanov I., Raje NS., Wolf J., DeAngelis LM., Makrutzki M., Riehl T., Pitcher B., Baselga J., Hyman DM.

Data di Pubblicazione: 2018-10-24

Abstract: Vemurafenib demonstrated evidence of durable antitumor activity in some patients with

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 30319400

DOI: doi.org/10.3389/fphar.2018.00950

Titolo: Metronomic Four-Drug Regimen Has Anti-tumor Activity in Pediatric Low-Grade Glioma; The Results of a Phase II Clinical Trial.

Autori: Verschuur A., Heng-Maillard MA., Dory-Lautrec P., Truillet R., Jouve E., Chastagner P., Leblond P., Aerts I., Honoré S., Entz-Werle N., Sirvent N., Gentet JC., Corradini N., André N.

Data di Pubblicazione: 2018-10-16

Abstract: None

Journal Title: Frontiers in pharmacology

PUBMED ID: 30253793

DOI: doi.org/10.1186/s40478-018-0602-5

Titolo: Tectal glioma as a distinct diagnostic entity: a comprehensive clinical, imaging, histologic and molecular analysis.

Autori: Liu APY., Harreld JH., Jacola LM., Gero M., Acharya S., Ghazwani Y., Wu S., Li X., Klimo P., Gajjar A., Chiang J., Qaddoumi I.

Data di Pubblicazione: 2018-9-27

Abstract: Tectal glioma (TG) is a rare low-grade tumor occurring predominantly in the pediatric population. There has been no detailed analysis of molecular alterations in TG. Risk factors associated with inferior outcome and long-term sequelae of TG have not been well-documented. We retrospectively studied TGs treated or referred for review at St. Jude Children's Research Hospital (SJCRH) between 1986 and 2013. Longitudinal clinical data were summarized, imaging and pathology specimen centrally reviewed, and tumor material analyzed with targeted molecular testing and genome-wide DNA methylation profiling. Forty-five patients with TG were included. Twenty-six (57.8%) were male. Median age at diagnosis was 9.9 years (range, 0.01-20.5). Median follow-up was 7.6 years (range, 0.5-17.0). The most common presenting symptoms were related to increased intracranial pressure. Of the 22 patients treated at SJCRH, 19 (86%) required cerebrospinal fluid diversion and seven (32%) underwent tumor-directed surgery. Five patients (23%) received radiation therapy and four (18%) systemic therapy. Ten-year overall and progression-free survival were 83.9±10.4% and 48.7±14.2%, respectively. Long-term morbidities included chronic headaches, visual symptoms and neurocognitive impairment. Lesion ≥3cm

Journal Title: Acta neuropathologica communications

PUBMED ID: 30227295

DOI: doi.org/10.1016/j.clineuro.2018.09.020

Titolo: How is stereotactic brain biopsy evolving? A multicentric analysis of a series of 421 cases treated in Rome over the last sixteen years.

Autori: Callovini GM., Telera S., Sherkat S., Sperduti I., Callovini T., Carapella CM.

Data di Pubblicazione: 2018-9-19

Abstract: Over the last sixteen years, we have witnessed a significant decrease in SBB procedures and a modification in target selection and histologic results. Despite the significant evolution of neuroimaging, an accurate non-invasive diagnosis of intracranial expanding lesions has not yet been achieved. Furthermore, the most recent WHO classification of brain tumors (2016),



which incorporates molecular and morphological features, has boosted the need for molecular processing of tissue samples in all expanding brain lesions. For these reasons, it is likely that SBBs will continue to be performed in specific cases, playing a significant role in diagnostic confirmation by providing tissue samples, so as to better assess the biology and the prognosis of cerebral lesions, as well as their sensitivity to standard radio-chemotherapy or to new molecular target therapies.

Journal Title: Clinical neurology and neurosurgery

PUBMED ID: 30220707

DOI: doi.org/10.1038/s41416-018-0251-2

Titolo: Brief Report: Potent clinical and radiological response to larotrectinib in TRK fusion-driven high-grade glioma.

Autori: Ziegler DS., Wong M., Mayoh C., Kumar A., Tsoi M., Mould E., Tyrrell V., Khuong-Quang DA., Pinese M., Gayevskiy V., Cohn RJ., Lau LMS., Reynolds M., Cox MC., Gifford A., Rodriguez M., Cowley MJ., Ekert PG., Marshall GM., Haber M.

Data di Pubblicazione: 2018-9-18

Abstract: Genes encoding TRK are oncogenic drivers in multiple tumour types including infantile fibrosarcoma, papillary thyroid cancer and high-grade gliomas (HGG). TRK fusions have a critical role in tumourigenesis in 40% of infant HGG. Here we report the first case of a TRK fusion-driven HGG treated with larotrectinib-the first selective pan-TRK inhibitor in clinical development. This 3-year-old girl had failed multiple therapies including chemotherapy and radiotherapy. Tumour profiling confirmed an ETV6-NTRK3 fusion. Treatment with larotrectinib led to rapid clinical improvement with near total resolution of primary and metastatic lesions on MRI imaging. This is the first report of a TRK fusion glioma successfully treated with a TRK inhibitor.

Journal Title: British journal of cancer

PUBMED ID: 30206764

DOI: doi.org/10.1007/s11060-018-2991-5

Titolo: Reirradiation and PD-1 inhibition with nivolumab for the treatment of recurrent diffuse intrinsic pontine glioma: a single-institution experience.

Autori: Kline C., Liu SJ., Duriseti S., Banerjee A., Nicolaides T., Raber S., Gupta N., Haas-Kogan D., Braunstein S., Mueller S.

Data di Pubblicazione: 2018-9-13

Abstract: Our experience demonstrates the tolerability of reRT with concurrent PD-1 inhibition for recurrent DIPG and suggests that combination therapy may offer survival benefit. Future prospective studies are needed to confirm the benefits of this combination therapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30203110

DOI: doi.org/10.1007/s00066-018-1358-3

Titolo: CT-guided interstitial HDR-brachytherapy for recurrent glioblastoma multiforme: a 20-year single-institute experience.

Autori: Chatzikonstantinou G., Zamboglou N., Archavlis E., Strouthos I., Zogala E., Milickovic N., Hilaris B., Baltas D., Rödel C., Tselis N.

Data di Pubblicazione: 2018-9-12

Abstract: For patients with recurrent GBM, interstitial HDR BRT is an effective re-irradiation method for even larger tumors providing palliation without excessive toxicity.

Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 30182159

DOI: doi.org/10.1007/s11060-018-2989-z

Titolo: Bevacizumab and re-irradiation for recurrent high grade gliomas: does sequence matter?

Autori: Palmer JD., Bhamidipati D., Song A., Eldredge-Hindy HB., Siglin J., Dan TD., Champ CE., Zhang I., Bar-Ad V., Kim L., Glass J., Evans JJ., Andrews DW., Werner-Wasik M., Shi W.

Data di Pubblicazione: 2018-9-6

Abstract: The combination of FSRT and BEV for recurrent/progressive HGG provides promising results in terms of overall survival and survival from recurrence. Combining these treatment modalities appears to improve upon the historic outcomes of either treatment alone. The outcomes data from this study support the ongoing RTOG trial exploring the combination of BEV and FSRT for recurrent HGG.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30137042

DOI: doi.org/10.17116/neiro201882487

Titolo: [Li-Fraumeni syndrome in a patient with multiple anaplastic oligodendrogliomas of the brain (a case report and literature review)].

Autori: Potapov AA., Abdilatipov AA., Okhlopkov VA., Gavrilov AG., Zakharova NE., Goryaynov SA., Kobayakov GL., Absalyamova OV., Kravchuk AD., Kulikov AS., Shugay SV., Nikitin PV., Batalov AI., Shelygin YA., Lyubchenko LN., Aliev MD., Spallone A.

Data di Pubblicazione: 2018-8-24

Abstract: An analysis of the literature and the clinical case indicate the success of multiple surgical interventions and chemotherapy courses performed for a long time in the patient with Li-Fraumeni syndrome manifested by colon adenocarcinoma, recurrent B-cell lymphoma, and multiple anaplastic oligodendroglioma of the brain. The patient had a good quality of life and returned to professional activity.

Journal Title: Zhurnal voprosy neirokhirurgii imeni N. N. Burdenko

PUBMED ID: 30107580

DOI: doi.org/10.1093/neuros/nyy365

Titolo: Is Visible Aminolevulinic Acid-Induced Fluorescence an Independent Biomarker for Prognosis in Histologically Confirmed (World Health Organization 2016) Low-Grade Gliomas?

Autori: Jaber M., Ewelt C., Wölfer J., Brokinkel B., Thomas C., Hasselblatt M., Grauer O., Stummer W.

Data di Pubblicazione: 2018-8-15

Abstract: This is the first report investigating the role of ALA-induced fluorescence in histologically confirmed LGG. Fluorescence appeared to be a marker for inherent malignant transformation and OS, independently of known prognostic markers. Fluorescence in LGG might be taken into account when deciding on adjuvant therapies.

Journal Title: Neurosurgery

PUBMED ID: 30097825

DOI: doi.org/10.1007/s11060-018-2972-8

Titolo: Impact of adjuvant treatments on survival in Korean patients with WHO grade II gliomas: KNOG 15-02 and KROG 16-04 intergroup study.

Autori: Koo T., Lim DH., Seol HJ., Dho YS., Kim IH., Chang JH., Lee J., Jung TY., Gwak HS., Cho KH., Hong CK., Lee IJ., Kim E., Kim JH., Hong YK., Jang HS., Kim CY., Kim IA., Kim SH., Kim YI., Kim EY., Kim WC., Hong S.

Data di Pubblicazione: 2018-8-12

Abstract: The achievement of GTR is important to improve survival in LGG patients. Adjuvant chemotherapy may enhance PFS, but adjuvant RT did not improve survival outcomes. After PSM, we observed potential impacts of adjuvant RT on PFS. Our results may reflect real-world practice and consequently may help to optimize treatment strategies for LGG.

Journal Title: Journal of neuro-oncology

PUBMED ID: 30094640

DOI: doi.org/10.1007/s00234-018-2060-y

Titolo: Glioblastoma radiomics: can genomic and molecular characteristics correlate with imaging response patterns?

Autori: Soike MH., McTyre ER., Shah N., Puchalski RB., Holmes JA., Paulsson AK., Miller LD., Cramer CK., Lesser GJ., Strowd RE., Hinson WH., Mott RT., Johnson AJ., Lo HW., Laxton AW., Tatter SB., Debinski W., Chan MD.

Data di Pubblicazione: 2018-8-11

Abstract: IR is associated with improved OS and PFS. The proneural subtype and MGMT methylated tumors had higher rates of IR.

Journal Title: Neuroradiology

PUBMED ID: 30071804

DOI: doi.org/10.4155/tde-2018-0022

Titolo: Nanotechnology-based strategies as novel therapies in gliomas.

Autori: Gaikwad PS., Banerjee R.

Data di Pubblicazione: 2018-8-4

Abstract: Gliomas are the most common malignancies of the brain and have a mean survival of 12 months with only 5-10% of the patients surviving for more than 5 years, independent of treatment after diagnosis. Conventional treatment modalities have found the modest success in reducing tumor burden and metastases. Presence of different biological barriers and drug-resistance efflux transporters are crucial for tumor recurrence and treatment failure. Nanotechnology may amend these circumstances by targeting residual infiltrating malignant cells with minimal damage to normal cells, on-demand release and an improved cellular uptake by tumor cells. This review highlights the current status and advances in nanotechnology for treatment of gliomas.

Journal Title: Therapeutic delivery

PUBMED ID: 30069427

DOI: doi.org/10.1016/j.nicl.2018.07.001

Titolo: Imaging biomarkers guided anti-angiogenic therapy for malignant gliomas.

Autori: Kong Z., Yan C., Zhu R., Wang J., Wang Y., Wang Y., Wang R., Feng F., Ma W.

Data di Pubblicazione: 2018-8-3

Abstract: Antiangiogenic therapy is a universal approach to the treatment of malignant gliomas but fails to prolong the overall survival of newly diagnosed or recurrent glioblastoma patients. Imaging biomarkers are quantitative imaging parameters capable of objectively describing biological processes, pathological changes and treatment responses in some situations and have been utilized for outcome predictions of malignant gliomas in anti-angiogenic therapy. Advanced magnetic resonance imaging techniques (including perfusion-weighted imaging and diffusion-weighted imaging), positron emission computed tomography and magnetic resonance spectroscopy are imaging techniques that can be used to acquire imaging biomarkers, including the relative cerebral blood volume (rCBV), K

Journal Title: NeuroImage. Clinical

PUBMED ID: 30054667

DOI: doi.org/10.1007/s00262-018-2214-0

Titolo: High-grade glioma associated immunosuppression does not prevent immune responses induced by therapeutic vaccines in combination with T

Autori: Löhr M., Freitag B., Technau A., Krauss J., Monoranu CM., Rachor J., Lutz MB., Hagemann C., Kessler AF., Linsenmann T., Wölfl M., Ernestus RI., Engelhardt S., Gelbrich G., Schlegel PG., Eyrich M.

Data di Pubblicazione: 2018-7-29

Abstract: High-grade gliomas (HGG) exert systemic immunosuppression, which is of particular importance as immunotherapeutic strategies such as therapeutic vaccines are increasingly used to treat HGGs. In a first cohort of 61 HGG patients we evaluated a panel of 30 hematological and 34 plasma biomarkers. Then, we investigated in a second cohort of 11 relapsed HGG patients receiving immunomodulation with metronomic cyclophosphamide upfront to a DC-based vaccine whether immune abnormalities persisted and whether they hampered induction of IFN $\gamma$

Journal Title: Cancer immunology, immunotherapy : CII

PUBMED ID: 30035459

DOI: doi.org/10.23736/S0390-5616.18.04463-6

Titolo: The prognostic improvement of add-on bevacizumab for progressive disease during concomitant temozolomide and radiation therapy in the patients with glioblastoma and anaplastic astrocytoma.

Autori: Yamaguchi S., Ishi Y., Motegi H., Okamoto M., Kobayashi H., Hirata K., Oda Y., Tanaka S., Terasaka S., Houkin K.

Data di Pubblicazione: 2018-7-24

Abstract: We found that, for patients with GBM/AAs whose tumors were continuously growing during radiotherapy, add-on BEV treatment resulted in survival benefits.

Journal Title: Journal of neurosurgical sciences

PUBMED ID: 30011045

DOI: doi.org/10.1093/neuros/nyy268

Titolo: Programmed Death Ligand 1 Is a Negative Prognostic Marker in Recurrent Isocitrate Dehydrogenase-Wildtype Glioblastoma.

Autori: Pratt D., Dominah G., Lobel G., Obungu A., Lynes J., Sanchez V., Adamstein N., Wang X., Edwards NA., Wu T., Maric D., Giles AJ., Gilbert MR., Quezado M., Nduom EK.

Data di Pubblicazione: 2018-7-17

Abstract: A 5% PD-L1 expression cut-off identified a subset of glioblastoma that is associated with a worse clinical outcome. This association remained significant within the newly defined IDH-wildtype classification. These findings could have implications for patient stratification in future clinical trials of PD-1/PD-L1 blockade.

Journal Title: Neurosurgery

PUBMED ID: 29997250

DOI: doi.org/10.1126/scitranslmed.aao3240

Titolo: CRISPR-enhanced engineering of therapy-sensitive cancer cells for self-targeting of primary and metastatic tumors.

Autori: Reinshagen C., Bhore D., Choi SH., Hutten S., Nesterenko I., Wakimoto H., Le Roux E., Rizvi A., Du W., Minicucci C., Shah K.

Data di Pubblicazione: 2018-7-13

Abstract: Tumor cells engineered to express therapeutic agents have shown promise to treat cancer. However, their potential to target cell surface receptors specific to the tumor site and their posttreatment fate have not been explored. We created therapeutic tumor cells expressing ligands specific to p

primary and recurrent tumor sites (receptor self-targeted tumor cells) and extensively characterized two different approaches using (i) therapy-resistant cancer cells, engineered with secretable death receptor-targeting ligands for "off-the-shelf" therapy in primary tumor settings, and (ii) therapy-sensitive cancer cells, which were CRISPR-engineered to knock out therapy-specific cell surface receptors before engineering with receptor self-targeted ligands and reapplied in autologous models of recurrent or metastatic disease. We show that both approaches allow high expression of targeted ligands that induce tumor cell killing and translate into marked survival benefits in mouse models of multiple cancer types. Safe elimination of therapeutic cancer cells after treatment was achieved by co-engineering with a prodrug-converting suicide system, which also allowed for real-time in vivo positron emission tomography imaging of therapeutic tumor cell fate. This study demonstrates self-tumor tropism of engineered cancer cells and their therapeutic potential when engineered with receptor self-targeted molecules, and it establishes a roadmap toward a safe clinical translation for different cancer types in primary, recurrent, and metastatic settings.

Journal Title: Science translational medicine

PUBMED ID: 29992434

DOI: doi.org/10.1007/s11060-018-2931-4

Titolo: Pineal region glioblastomas display features of diffuse midline and non-midline gliomas.

Autori: D'Amico RS., Zanazzi G., Wu P., Canoll P., Bruce JN.

Data di Pubblicazione: 2018-7-12

Abstract: This study expands the clinical and pathologic spectrum of pineal region GBM, and provides the first report of the genetic landscape of these tumors.

Journal Title: Journal of neuro-oncology

PUBMED ID: 29990975

DOI: doi.org/10.1159/000469681

Titolo: Novel and Prospective Molecular Targets for Therapy of Intracranial Gliomas.

Autori: Butowski N.

Data di Pubblicazione: 2018-7-11

Abstract: Multiple alterations in the expression levels of genes or proteins have been identified in gliomas, including activation of oncogenes and silencing of tumor suppressor genes. Illuminating these molecular mechanisms of tumorigenesis and treatment resistance is necessary for the development of new therapies. With the promise of better effectiveness and less toxicity, the emphasis in drug development has moved from cytotoxic, non-specific chemotherapies to molecular targeted agents. However, despite progress in other areas of oncology, targeted therapy success stories in cases of brain tumors remain all but absent. Nonetheless, experiences from previous clinical trials suggest that a small number of unselected patients may benefit from such treatment. An increasing knowledge about related factors and prospective enrichment strategies now shape research and clinical trial design in neuro-oncology and may lead to improved outcomes after molecular targeted therapies of gliomas.

Journal Title: Progress in neurological surgery

PUBMED ID: 29980414

DOI: doi.org/10.1016/j.ijrobp.2018.04.045

Titolo: Combining Perfusion and High B-value Diffusion MRI to Inform Prognosis and Predict Failure Patterns in Glioblastoma.

Autori: Wahl DR., Kim MM., Aryal MP., Hartman H., Lawrence TS., Schipper MJ., Parmar HA., Cao Y.  
Data di Pubblicazione: 2018-7-8  
Abstract: TV  
Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 29980179  
DOI: doi.org/10.1186/s12883-018-1099-z  
Titolo: Clinical characteristics and short-term prognosis of LGI1 antibody encephalitis: a retrospective case study.  
Autori: Li W., Wu S., Meng Q., Zhang X., Guo Y., Cong L., Cong S., Zheng D.  
Data di Pubblicazione: 2018-7-8  
Abstract: Primary symptoms of LGI1 antibody encephalitis include memory impairments, seizures, FBDS, and mental and behavioral abnormalities. Increased titers of LGI1 antibodies are also present in the serum/CSF of patients. Patients often have hyponatremia, and MRIs show abnormalities in various brain regions. Finally, immunotherapy shows good efficacy and positive benefits, although patients may relapse in the short-term.  
Journal Title: BMC neurology

PUBMED ID: 29979390  
DOI: doi.org/10.1097/MD.00000000000011254  
Titolo: High-dose fotemustine in temozolomide-pretreated glioblastoma multiforme patients: A phase I/II trial.  
Autori: Marinelli A., Lamberti G., Cerbone L., Cordua N., Buonerba C., Peluso G., Di Lorenzo G., De Placido S.  
Data di Pubblicazione: 2018-7-7  
Abstract: We conclude that fotemustine can be safely administered at 120mg/m biweekly. The efficacy of such modified schedule and doses should be compared to the biweekly schedule at 80mg and the standard weekly schedule at 80 to 100mg/m.  
Journal Title: Medicine

PUBMED ID: 29953370  
DOI: doi.org/10.1615/CritRevOncog.2018025740  
Titolo: Radiation-Induced Gliomas.  
Autori: Aherne NJ., Murphy BM.  
Data di Pubblicazione: 2018-6-29  
Abstract: Radiation therapy has been a cornerstone of cancer management for many decades and is an integral part of the multi-modality care of patients with brain tumors. The known serious side effects of radiation therapy on the head or central nervous system are uncommon and include radiation necrosis, microangiopathy, and progressive leukencephalopathy. In addition, there have been descriptions of radiation-induced tumors including sarcomas, gliomas, lymphomas, and carcinomas of the thyroid. Patients who have received radiation therapy of the head or face may rarely develop radiation-induced tumors, a majority of which are meningiomas, followed by radiation-induced gliomas (RIGs) and sarcomas. The increased risk of RIGs is well described in both the pediatric and adult populations and after the use of both therapeutic and diagnostic radiations. The incidence of RIGs is estimated at approximately 0.5-2.7% at a latent period of approximately 15 years. The risk appears to be dependent on patient age at treatment, as well as radiation dose and treatment volume considerations. The scope of this review focuses on the etiology, clinical features, and management of RIGs as they relate to previous radiation therapy.  
Journal Title: Critical reviews in oncogenesis

PUBMED ID: 29949160

DOI: doi.org/10.26355/eurev\_201806\_15268

Titolo: MicroRNA-378 acts as a prognosis marker and inhibits cell migration, invasion and epithelial-mesenchymal transition in human glioma by targeting IRG1.

Autori: Shi HZ., Wang D., Sun XN., Sheng L.

Data di Pubblicazione: 2018-6-28

Abstract: We showed that the suppressive role of miR-378 in glioma, which was regulated by IRG1, suggested that the miR-378/IRG1 axis may be an effective target for glioma treatment.

Journal Title: European review for medical and pharmacological sciences

PUBMED ID: 29943141

DOI: doi.org/10.1007/s10143-018-0996-3

Titolo: IDH wild-type WHO grade II diffuse low-grade gliomas. A heterogeneous family with different outcomes. Systematic review and meta-analysis.

Autori: Di Carlo DT., Duffau H., Cagnazzo F., Benedetto N., Morganti R., Perini P.

Data di Pubblicazione: 2018-6-27

Abstract: WHO grade II diffuse low-grade gliomas (DLGGs) were recently divided into sub-groups on the basis of their molecular profiles. IDH wild-type (IDH-wt) tumors seem to be associated with unfavorable prognoses due to biological similarities to glioblastomas. The authors performed a systematic review and meta-analysis of literature examining epidemiology, clinical characteristics, management, and the outcome of IDH-wt grade II DLGGs. According to PRISMA guidelines, a comprehensive review of studies published from January 2009 to October 2017 was carried out. The authors identified series that examined the prevalence rate, clinical and radiological characteristics, treatment, and outcome of IDH-wt DLGGs. Variables influencing outcomes were analyzed using a random-effects meta-analysis model. Finally, a meta-regression analysis was performed to examine the impact of therapeutic strategies on the effect-size. Twenty-two studies were included in this systematic review. The IDH-wt prevalence rate was 22.9% (95% CI 18.4-27.4%). The hazard ratio for this molecular subgroup in the DLGGs population was 3.46 (95% CI 2.24-5.36;  $p < 0.001$ ), and the heterogeneity was significant ( $I^2 = 75.3\%$ ).

Journal Title: Neurosurgical review

PUBMED ID: 29942135

DOI: doi.org/10.2147/OTT.S160685

Titolo: Effectiveness of lomustine and bevacizumab in progressive glioblastoma: a meta-analysis.

Autori: Song J., Xue YQ., Zhao MM., Xu P.

Data di Pubblicazione: 2018-6-27

Abstract: Although treatment with CCNU plus BEV prolonged PFS, it did not confer OS advantage over monotherapies in patients with progressive GBM. The encouraging results of the addition of CCNU to BEV warrant investigation in further randomized trials.

Journal Title: OncoTargets and therapy

PUBMED ID: 29927794

DOI: doi.org/10.1097/MPH.0000000000001241

Titolo: Clinical Characteristics and Outcome of Children With Relapsed Medulloblastoma: A Retrospective Study at a Single Center in China.

Autori: Du S., Yang S., Zhao X., Xiao J., Ren S., Li S., Zhang J., Wang Y., Gong X., Li M., Sun Y., Wu W., Sun L.

Data di Pubblicazione: 2018-6-22

Abstract: Relapsed medulloblastoma (MB) has a dire prognosis, and chemotherapy remains the main therapeutic option. We retrospectively analyzed the clinical characteristics and survival rates of 60 Chinese children with relapsed MB. The patients received 11 cycles of chemotherapy in sequence, followed by 12 cycles of oral temozolomide and etoposide. Thirty patients were simultaneously administered intrathecal methotrexate (IT-MTX). The Kaplan-Meier method was used to determine survival rates; the patients' median survival time after relapse was 2.8 years, 5-year progression-free survival (PFS) and overall survival (OS) rates were  $26.7\pm 5.7\%$  and  $31.6\pm 6.9\%$ , respectively. There was no significant difference between these rates according to histology or molecular subgroup. Tumor cells were detected in the cerebrospinal fluid of over 40% of patients; such patients had significantly shorter OS and PFS rates. Patients who received IT-MTX showed significantly longer survival than those who did not (3.73 vs. 2.06y, respectively,  $P=0.000$ ); the corresponding 5-year PFS and OS rates were  $43.3\pm 9.0\%$  versus  $10.0\pm 5.5\%$  and  $49.5\pm 11.1\%$  versus  $14.6\pm 6.9\%$ , respectively ( $P=0.000$ ). In addition, tumor cell-positive cerebrospinal fluid and IT-MTX use significantly influenced PFS and OS in relapsed patients. Taken together, our data show that IT-MTX improves the survival of patients with relapsed MB.

Journal Title: Journal of pediatric hematology/oncology

PUBMED ID: 29879076

DOI: doi.org/10.1097/MD.00000000000011072

Titolo: Primary central nervous system lymphoma in a patient with systemic lupus erythematosus mimicking high-grade glioma: A case report and review of literature.

Autori: Su L., Ding M., Chen L., Li C., Lao M.

Data di Pubblicazione: 2018-6-8

Abstract: PCNSL in immunocompromised hosts may present heterogeneous contrast enhancement, which should be differentiated from other diseases especially high-grade glioma.

Journal Title: Medicine

PUBMED ID: 29868932

DOI: doi.org/10.1007/s00381-018-3842-6

Titolo: Is there an increased risk of spinal relapse in standard-risk medulloblastoma/primitive neuroectodermal tumor patients who receive only a reduced dose of craniospinal radiotherapy?

Autori: Burcu A., Nazan Ç., Özgür Ö., Serra K., Mehmet K., Serap A., Bengü D., Canan V., Haldun Ö., Savaş K., Tuncer T., Taner A., Yeşim E., Ömer K., Yavuz A.

Data di Pubblicazione: 2018-6-6

Abstract: The risk of isolated spinal relapse does not increase with reduced-dose craniospinal RT, since there is no isolated relapse in either the standard or high-risk groups of patients.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 29868485

DOI: doi.org/10.3389/fonc.2018.00169

Titolo: The Integration of Biology Into the Treatment of Diffuse Intrinsic Pontine Glioma: A Review of the North American Clinical Trial Perspective.

Autori: Clymer J., Kieran MW.



Data di Pubblicazione: 2018-6-6

Abstract: Dramatic advances in the molecular analysis of diffuse intrinsic pontine glioma have occurred over the last decade and resulted in the identification of potential therapeutic targets. In spite of these advances, no significant improvement in the outcome has been achieved and median survival remains approximately 10 months. An understanding of the approaches that have been taken to date, why they failed, and how that information can lead the field forward is critical if we are to change the

Journal Title: Frontiers in oncology

PUBMED ID: 29855771

DOI: doi.org/10.1007/s11060-018-2910-9

Titolo: Mono-exponential, diffusion kurtosis and stretched exponential diffusion MR imaging response to chemoradiation in newly diagnosed glioblastoma.

Autori: Chakhoyan A., Woodworth DC., Harris RJ., Lai A., Nghiemphu PL., Liao LM., Pope WB., Cloughesy TF., Ellingson BM.

Data di Pubblicazione: 2018-6-2

Abstract: Despite increased tissue complexity following chemoradiation, advanced diffusion models have longer acquisition times, provide largely comparable measures of diffusivity, and do not appear to provide additional prognostic value compared to mono-exponential ADC maps.

Journal Title: Journal of neuro-oncology

PUBMED ID: 29788980

DOI: doi.org/10.1186/s13256-018-1680-5

Titolo: Treatment of ventriculoperitoneal shunt infection and ventriculitis caused by *Acinetobacter baumannii*: a case report.

Autori: Demoz GT., Alebachew M., Legesse Y., Ayalneh B.

Data di Pubblicazione: 2018-5-24

Abstract: We presented our case of pandrug-resistant *A. baumannii* ventriculoperitoneal shunt infection and ventriculitis successfully treated with a systemic ampicillin-sulbactam. Provision of systemic ampicillin-sulbactam should not be undermined. Therefore, this case exemplifies that intravenous administration of ampicillin-sulbactam can be a good therapeutic option against *A. baumannii* ventriculoperitoneal shunt infection and ventriculitis.

Journal Title: Journal of medical case reports

PUBMED ID: 29779086

DOI: doi.org/10.1007/s11060-018-2907-4

Titolo: Retrospective study of nivolumab for patients with recurrent high grade gliomas.

Autori: Mantica M., Pritchard A., Lieberman F., Drappatz J.

Data di Pubblicazione: 2018-5-21

Abstract: Treatment with nivolumab therapy was associated with a manageable safety profile. In a subset of patients, there was disease stabilization in heavily pre-treated recurrent HGG.

Journal Title: Journal of neuro-oncology

PUBMED ID: 29774180

DOI: doi.org/10.21037/qims.2018.04.05

Titolo: Survival prediction based on qualitative MRI diffusion signature in patients with recurrent high grade glioma treated with bevacizumab.

Autori: Goyal P., Tenenbaum M., Gupta S., Kochar PS., Bhatt AA., Mangla M., Kumar Y., Mangla R.

Data di Pubblicazione: 2018-5-19

Abstract: In patients with recurrent glioma treated with bevacizumab, the presence of homogenous dark signal (FDR  
Journal Title: Quantitative imaging in medicine and surgery

PUBMED ID: 29764702

DOI: doi.org/10.1016/j.jocn.2018.04.077

Titolo: A novel neuromodulation technique for the rehabilitation of balance and gait: A case study.

Autori: Cofré Lizama LE., Bastani A., Panisset MG., Drummond K., Khan F., Galea MP.

Data di Pubblicazione: 2018-5-17

Abstract: Cranial-nerve non-invasive neuromodulation (CN-NINM) through the tongue has been proposed as an adjuvant intervention to improve efficacy of rehabilitation. However, CN-NINM effects have only been explored in multiple sclerosis and stroke populations. In this report we used CN-NINM during a 2-week (2×1.5h sessions daily) physiotherapy program for the rehabilitation of a 57 y/o woman presenting with balance and gait impairments after a surgical resection of a fourth ventricular ependymoma. Clinical and instrumented balance and gait assessments showed improved performance in all tests and without adverse effects. This study shows the beneficial effects and feasibility of combined physiotherapy and CN-NINM in this patient.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 29753958

DOI: doi.org/10.1016/j.jconrel.2018.05.008

Titolo: Drug delivery challenges and future of chemotherapeutic nanomedicine for glioblastoma treatment.

Autori: Ganipineni LP., Danhier F., Préat V.

Data di Pubblicazione: 2018-5-14

Abstract: Glioblastoma (GBM) is one of the most aggressive and deadliest central nervous system tumors, and the current standard treatment is surgery followed by radiotherapy with concurrent chemotherapy. Nevertheless, the survival period is notably low. Although ample research has been performed to develop an effective therapeutic strategy for treating GBM, the success of extending patients' survival period and quality of life is limited. This review focuses on the strategies developed to address the challenges associated with drug delivery in GBM, particularly nanomedicine. The first part describes major obstacles to the development of effective GBM treatment strategies. The second part focuses on the conventional chemotherapeutic nanomedicine strategies, their limitations and the novel and advanced strategies of nanomedicine, which could be promising for GBM treatment. We also highlighted the prominence of nanomedicine clinical translation. The near future looks bright following the beginning of clinical translation of nanochemotherapy for GBM.

Journal Title: Journal of controlled release : official journal of the Controlled Release Society

PUBMED ID: 29752148

DOI: doi.org/10.1016/j.neuchi.2017.12.007

Titolo: Malignant primary diffuse leptomeningeal gliomatosis with histone H3 .3 K27M mutation.

Autori: Champeaux C., Drier A., Devaux B., Tauziède-Espariat A.

Data di Pubblicazione: 2018-5-13

Abstract: MPLG is a rare tumor which should be considered whenever a patient presents with diffuse or multinodular meningeal contrast-enhancing lesions. Some cases of MPLG share histological and immunophenotypical features with d

diffuse midline gliomas H3-K27M-mutant, a rapidly fatal disease. The diagnosis remains histopathological and, therefore a biopsy is obligatory without delay. Immunohistochemistry and/or molecular analyses are now currently essential for a formal classification and, to provide a better prediction of clinical outcome, particularly in this heterogeneous group of tumors.

Journal Title: Neuro-Chirurgie

PUBMED ID: 29712977

DOI: doi.org/10.1038/s41598-018-25169-2

Titolo: Concordant association validates MGMT methylation and protein expression as favorable prognostic factors in glioma patients on alkylating chemotherapy (Temozolomide).

Autori: Pandith AA., Qasim I., Zahoor W., Shah P., Bhat AR., Sanadhya D., Shah ZA., Naikoo NA.

Data di Pubblicazione: 2018-5-2

Abstract: 0

Journal Title: Scientific reports

PUBMED ID: 29687258

DOI: doi.org/10.1007/s00401-018-1849-4

Titolo: Novel, improved grading system(s) for IDH-mutant astrocytic gliomas.

Autori: Shirahata M., Ono T., Stichel D., Schrimpf D., Reuss DE., Sahm F., Koelsche C., Wefers A., Reinhardt A., Huang K., Sievers P., Shimizu H., Nanjo H., Kobayashi Y., Miyake Y., Suzuki T., Adachi JI., Mishima K., Sasaki A., Nishikawa R., Bewerunge-Hudler M., Ryzhova M., Absalyamova O., Golanov A., Sinn P., Platten M., Jungk C., Winkler F., Wick A., Hänggi D., Unterberg A., Pfister SM., Jones DTW., van den Bent M., Hegi M., French P., Baumert BG., Stupp R., Gorlia T., Weller M., Capper D., Korshunov A., Herold-Mende C., Wick W., Louis DN., von Deimling A.

Data di Pubblicazione: 2018-4-25

Abstract: According to the 2016 World Health Organization Classification of Tumors of the Central Nervous System (2016 CNS WHO), IDH-mutant astrocytic gliomas comprised WHO grade II diffuse astrocytoma, IDH-mutant (AII

Journal Title: Acta neuropathologica

PUBMED ID: 29676695

DOI: doi.org/10.3171/2017.10.JNS171825

Titolo: Huge heterogeneity in survival in a subset of adult patients with resected, wild-type isocitrate dehydrogenase status, WHO grade II astrocytomas.

Autori: Poulen G., Gozé C., Rigau V., Duffau H.

Data di Pubblicazione: 2018-4-21

Abstract: OBJECTIVEWorld Health Organization grade II gliomas are infiltrating tumors that inexorably progress to a higher grade of malignancy. However, the time to malignant transformation is quite unpredictable at the individual patient level. A wild-type isocitrate dehydrogenase (IDH-wt) molecular profile has been reported as a poor prognostic factor, with more rapid progression and a shorter survival compared with IDH-mutant tumors. Here, the oncological outcomes of a series of adult patients with IDH-wt, diffuse, WHO grade II astrocytomas (AII) who underwent resection without early adjuvant therapy were investigated.METHODSA retrospective review of patients extracted from a prospective database who underwent resection between 2007 and 2013 for histopathologically confirmed, IDH-wt, non-1p19q codeleted AII was performed. All patients had a minimum follow-up period of 2 years. Information regarding clinical, radiographic, and surgical results and survival were collected and analyzed.RESULTSThirty-one consecutive patients (18 men and 13 women, median age 39.6 years) were included in this study. The preoperative median tumor v

volume was 54 cm<sup>3</sup> (range 3.5-180 cm<sup>3</sup>). The median growth rate, measured as the velocity of diametric expansion, was 2.45 mm/year. The median residual volume after surgery was 4.2 cm<sup>3</sup> (range 0-30 cm<sup>3</sup>) with a median volumetric extent of resection of 93.97% (8 patients had a total or supratotal resection). No patient experienced permanent neurological deficits after surgery, and all patients resumed a normal life. No immediate postoperative chemotherapy or radiation therapy was given. The median clinical follow-up duration from diagnosis was 74 months (range 27-157 months). In this follow-up period, 18 patients received delayed chemotherapy and/or radiotherapy for tumor progression. Five patients (16%) died at a median time from radiological diagnosis of 3.5 years (range 2.6-4.5 years). Survival from diagnosis was 77.27% at 5 years. None of the 21 patients with a long-term follow-up greater than 5 years have died. There were no significant differences between the clinical, radiological, or molecular characteristics of the survivors relative to the patients who died.

**CONCLUSIONS** Huge heterogeneity in the survival data for a subset of 31 patients with resected IDH-wt AII tumors was observed. These findings suggest that IDH mutation status alone is not sufficient to predict risk of malignant transformation and survival at the individual level. Therefore, the therapeutic management of AII tumors, in particular the decision to administer early adjuvant chemotherapy and/or radiation therapy following surgery, should not solely rely on routine molecular markers.

Journal Title: Journal of neurosurgery

PUBMED ID: 29637509

DOI: doi.org/10.1007/s11060-018-2847-z

Titolo: Safety, efficacy and survival of patients with primary malignant brain tumours (PMBT) in phase I (Ph1) trials: the 12-year Royal Marsden experience.

Autori: Coleman N., Michalarea V., Alken S., Rihawi K., Lopez RP., Tunariu N., Petruckevitch A., Molife LR., Banerji U., De Bono JS., Welsh L., Saran F., Lopez J.

Data di Pubblicazione: 2018-4-12

Abstract: We report a survival benefit for patients with PMBT treated on Ph1 trials. Toxicity and efficacy outcomes were comparable to the general Ph1 population. In the absence of an internationally recognized standard second line treatment for patients with recurrent PMBT, more Ph1 trials should allow enrolment of patients with refractory PMBT and Ph1 trial participation should be considered at an earlier stage.

Journal Title: Journal of neuro-oncology

PUBMED ID: 29632053

DOI: doi.org/10.6004/jnccn.2017.7052

Titolo: Concurrent BRAF/MEK Inhibitors in

Autori: Schreck KC., Guajardo A., Lin DDM., Eberhart CG., Grossman SA.

Data di Pubblicazione: 2018-4-11

Abstract: None

Journal Title: Journal of the National Comprehensive Cancer Network : JNCCN

PUBMED ID: 29619962

DOI: doi.org/10.1016/j.ijrobp.2018.01.048

Titolo: A Prospective 4n Radiation Therapy Clinical Study in Recurrent High-Grade Glioma Patients.

Autori: Yu VY., Landers A., Woods K., Nguyen D., Cao M., Du D., Chin RK., Sheng K., Kaprelian TB.

Data di Pubblicazione: 2018-4-6

Abstract: The feasibility, safety, dosimetric benefits, delivery efficiency, and patient comfort of 4n radiation therapy have been clinically demonstrate

d with a prospective clinical trial. The results elucidate the potential and challenges of wider clinical implementations.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 29594657

DOI: doi.org/10.1007/s11060-018-2820-x

Titolo: A predictive value of von Willebrand factor for early response to Bevacizumab therapy in recurrent glioma.

Autori: Pace A., Mandoj C., Antenucci A., Villani V., Sperduti I., Casini B., Carosi M., Fabi A., Vidiri A., Koudriavtseva T., Conti L.

Data di Pubblicazione: 2018-3-30

Abstract: Bevacizumab (BV), a neutralizing monoclonal antibody against the vascular endothelial growth factor ligand, is recognized as a potent anti-angiogenic agent with antitumor activity. The aim of this single-center, retrospective, longitudinal study was to investigate the possible predictive value of baseline demographic, clinical and laboratory parameters for early 3-month response to BV therapy in patients with recurrent glioma. Forty-nine patients with recurrent glioma received BV at 10 mg/kg intravenously every 3 weeks alone or in association with chemotherapy were included in this study. Blood samples were collected from all patients before the first (baseline), the second and the third administration of BV. After 3 months of BV therapy, patients with partial response were defined as responders whereas patients with stable or progressive disease were defined as non-responders. The median overall follow-up was 8 months (range 1-73), the median overall survival (OS) was 8 months (95% CI 6-10) and the median progression free survival (PFS) was 4 months (95% CI 3-5). Thirty-five % of patients were responders and showed significantly lower von Willebrand factor (VWF) levels than non-responders at all sample times ( $p < .02$  for all). Also, on multivariate analysis the baseline VWF value was the only predictor for an early response to BV therapy. Furthermore, D-dimer and prothrombin fragment 1+2 were predictive factors for OS while Karnofsky performance status resulted predictive for PFS. VWF antigen value is a possible predictive biomarker for an early 3-month response to BV therapy in recurrent glioma.

Journal Title: Journal of neuro-oncology

PUBMED ID: 29572492

DOI: doi.org/10.1038/s41598-018-22739-2

Titolo: Radiomic MRI signature reveals three distinct subtypes of glioblastoma with different clinical and molecular characteristics, offering prognostic value beyond IDH1.

Autori: Rathore S., Akbari H., Rozycki M., Abdullah KG., Nasrallah MP., Binder ZA., Davuluri RV., Lustig RA., Dahmane N., Bilello M., O'Rourke DM., Datzikos C.

Data di Pubblicazione: 2018-3-25

Abstract: The remarkable heterogeneity of glioblastoma, across patients and over time, is one of the main challenges in precision diagnostics and treatment planning. Non-invasive in vivo characterization of this heterogeneity using imaging could assist in understanding disease subtypes, as well as in risk-stratification and treatment planning of glioblastoma. The current study leveraged advanced imaging analytics and radiomic approaches applied to multi-parametric MRI of de novo glioblastoma patients (n=208 discovery, n=53 replication), and discovered three distinct and reproducible imaging subtypes of glioblastoma, with differential clinical outcome and underlying molecular characteristics, including isocitrate dehydrogenase-1 (IDH1), O

Journal Title: Scientific reports

PUBMED ID: 29559563

DOI: doi.org/10.1158/1078-0432.CCR-17-1775

Titolo: Phase I Study of MEDI3617, a Selective Angiopoietin-2 Inhibitor Alone and Combined with Carboplatin/Paclitaxel, Paclitaxel, or Bevacizumab for Advanced Solid Tumors.

Autori: Hyman DM., Rizvi N., Natale R., Armstrong DK., Birrer M., Recht L., Dotan E., Makker V., Kaley T., Kuruvilla D., Gribbin M., McDevitt J., Lai DW., Dar M.

Data di Pubblicazione: 2018-3-22

Abstract: None

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 29557060

DOI: doi.org/10.1007/s11060-018-2831-7

Titolo: JCOG0911 INTEGRA study: a randomized screening phase II trial of interferon $\beta$  plus temozolomide in comparison with temozolomide alone for newly diagnosed glioblastoma.

Autori: Wakabayashi T., Natsume A., Mizusawa J., Katayama H., Fukuda H., Sumi M., Nishikawa R., Narita Y., Muragaki Y., Maruyama T., Ito T., Beppu T., Nakamura H., Kayama T., Sato S., Nagane M., Mishima K., Nakasu Y., Kurisu K., Yamasaki F., Sugiyama K., Onishi T., Iwadate Y., Terasaki M., Kobayashi H., Matsumura A., Ishikawa E., Sasaki H., Mukasa A., Matsuo T., Hirano H., Kumabe T., Shinoura N., Hashimoto N., Aoki T., Asai A., Abe T., Yoshino A., Arakawa Y., Asano K., Yoshimoto K., Shibui S., Shibui S.

Data di Pubblicazione: 2018-3-21

Abstract: TMZ+IFN $\beta$ +RT is not considered as a candidate for the following phase III trial, and TMZ+RT remained to be a most promising treatment. This trial was registered with the UMIN Clinical Trials Registry: UMIN000003466.

Journal Title: Journal of neuro-oncology

PUBMED ID: 29551724

DOI: doi.org/10.1016/j.wneu.2018.03.069

Titolo: The Effectiveness of Salvage Treatments for Recurrent Lesions of Oligodendrogliomas Previously Treated with Upfront Chemotherapy.

Autori: Kuga D., Hata N., Akagi Y., Amemiya T., Sangatsuda Y., Hatae R., Yoshimoto K., Mizoguchi M., Iihara K.

Data di Pubblicazione: 2018-3-20

Abstract: In isocitrate dehydrogenase-mutant and 1p/19q-codeleted oligodendrogliomas, most of the tumors that demonstrated early progression appeared as local, nonlethal lesions, which have been well-controlled by salvage treatments. A precise diagnosis of oligodendrogliomas using molecular parameters is crucial to receive the best benefit from salvage treatment.

Journal Title: World neurosurgery

PUBMED ID: 29540809

DOI: doi.org/10.1038/s41598-018-22697-9

Titolo: Retrospective Analysis of Radiological Recurrence Patterns in Glioblastoma, Their Prognostic Value And Association to Postoperative Infarct Volume.

Autori: Bette S., Barz M., Huber T., Straube C., Schmidt-Graf F., Combs SE., Delbridge C., Gerhardt J., Zimmer C., Meyer B., Kirschke JS., Boeckh-Behrens T., Wiestler B., Gempt J.

Data di Pubblicazione: 2018-3-16

Abstract: Recent studies suggested that postoperative hypoxia might trigger invasive tumor growth, resulting in diffuse/multifocal recurrence patterns.

Aim of this study was to analyze distinct recurrence patterns and their association to postoperative infarct volume and outcome. 526 consecutive glioblastoma patients were analyzed, of which 129 met our inclusion criteria: initial tumor diagnosis, surgery, postoperative diffusion-weighted imaging and tumor recurrence during follow-up. Distinct patterns of contrast-enhancement at initial diagnosis and at first tumor recurrence (multifocal growth/progression, contact to dura/ventricle, ependymal spread, local/distant recurrence) were recorded by two blinded neuroradiologists. The association of radiological patterns to survival and postoperative infarct volume was analyzed by univariate/multivariate survival analyses and binary logistic regression analysis. With increasing postoperative infarct volume, patients were significantly more likely to develop multifocal recurrence, recurrence with contact to ventricle and contact to dura. Patients with multifocal recurrence (Hazard Ratio (HR) 1.99,  $P=0.010$ ) had significantly shorter OS, patients with recurrent tumor with contact to ventricle (HR 1.85,  $P=0.036$ ), ependymal spread (HR 2.97,  $P=0.004$ ) and distant recurrence (HR 1.75,  $P=0.019$ ) significantly shorter post-progression survival in multivariate analyses including well-established prognostic factors like age, Karnofsky Performance Score (KPS), therapy, extent of resection and patterns of primary tumors. Postoperative infarct volume might initiate hypoxia-mediated aggressive tumor growth resulting in multifocal and diffuse recurrence patterns and impaired survival.

Journal Title: Scientific reports

PUBMED ID: 29524050

DOI: [doi.org/10.1007/s12035-018-0978-z](https://doi.org/10.1007/s12035-018-0978-z)

Titolo: Role of Chimeric Antigen Receptor T Cell Therapy in Glioblastoma Multiforme.

Autori: Jindal V.

Data di Pubblicazione: 2018-3-11

Abstract: Glioblastoma multiforme (GBM) is the most common primary malignant cancer of brain, which is extremely aggressive and carries a dreadful prognosis. Current treatment protocol runs around radiotherapy, surgical resection, and temozolomide with median overall survival of around 12-15 months. Due to its heterogeneity and mutational load, immunotherapy with chimeric antigen receptor (CAR) T cell therapy can be a promising treatment option for recurrent glioblastoma. Initial phase I studies have shown that this therapy is safe without dose-limiting side effects and it also has a better clinical outcome. Therefore, CAR T cell therapy can be a great future tool in our armamentarium to treat advanced GBM. In this article, we have explained the structure, mechanism of action, and rationale of CAR T cell therapy in GBM; we also discussed various antigenic targets and clinical outcome of initial studies of this novel therapy.

Journal Title: Molecular neurobiology

PUBMED ID: 29522936

DOI: [doi.org/10.1016/j.clineuro.2018.02.027](https://doi.org/10.1016/j.clineuro.2018.02.027)

Titolo: Evaluation of DNA ploidy with intraoperative flow cytometry may predict long-term survival of patients with supratentorial low-grade gliomas: Analysis of 102 cases.

Autori: Suzuki A., Maruyama T., Nitta M., Komori T., Ikuta S., Chernov M., Tamura M., Kawamata T., Muragaki Y.

Data di Pubblicazione: 2018-3-10

Abstract: DNA ploidy assessed with iFC may be effectively used as prognostic indicator in cases of LGG, especially of DA. Aneuploid tumors demonstrate more aggressive clinical course translated into shorter OS of patients. Thus, their detection during surgery may be helpful for decision on the optimal EO R, and for choice of the most appropriate postoperative adjuvant therapy.

Journal Title: Clinical neurology and neurosurgery

PUBMED ID: 29511977

DOI: doi.org/10.1007/s11060-018-2815-7

Titolo: Patterns of relapse for children with localized intracranial ependymoma.

Autori: De B., Khakoo Y., Souweidane MM., Dunkel IJ., Patel SH., Gilheeney S W., De Braganca KC., Karajannis MA., Wolden SL.

Data di Pubblicazione: 2018-3-8

Abstract: We examined patterns of relapse and prognostic factors in children with intracranial ependymoma. Records of 82 children diagnosed with localized intracranial ependymoma were reviewed. 52% first presented to our institution after relapse. Median age at initial diagnosis was 4 years (range 0-18 years). Gender was 55% male. Initial tumor location was infratentorial in 71% and supratentorial in 29%. Histology was WHO Grade II in 32% and Grade III in 68%. As part of definitive management, 99% had surgery, 70% received RT (26% 2D/3D-conformal RT[CRT], 22% intensity-modulated RT [IMRT], 22% proton), and 37% received chemotherapy. Median follow-up was 4.6 years (range 0.2-32.9). Overall, 74% of patients relapsed (50% local, 17% distant, 7% local+distant) at a median 1.5 (range 0.1-17.5) years. Five-year OS and FFS for patients presenting prior to relapse are 70% (95% confidence interval [CI], 50-83%) and 48% (95% CI 30-64%), respectively. On log-rank, superior overall survival (OS) was demonstrated for gross total resection ( $p=0.03$ ). Superior failure-free survival (FFS) was demonstrated for age $<5$  years ( $p=0.04$ ). No difference in OS or FFS was found between 2D/3D-CRT versus IMRT/proton ( $p>0.05$ ). On multivariate analysis, age $\leq 5$  was independently associated with a lower risk of death and failure versus older patients ( $p<0.05$ ). Contrary to previous reports, young age may not be a poor prognostic factor in patients who can tolerate intensive treatment. Future studies examining patients stratified by clinical and molecular attributes are warranted.

Journal Title: Journal of neuro-oncology

PUBMED ID: 29492119

DOI: doi.org/10.4103/ajns.AJNS\_95\_17

Titolo: Significant Effect of Anti-tyrosine Kinase Inhibitor (Gefitinib) on Overall Survival of the Glioblastoma Multiforme Patients in the Backdrop of Mutational Status of Epidermal Growth Factor Receptor and

Autori: Arif SH., Pandith AA., Tabasum R., Ramzan AU., Singh S., Siddiqi MA., Bhat AR.

Data di Pubblicazione: 2018-3-2

Abstract: We conclude that

Journal Title: Asian journal of neurosurgery

PUBMED ID: 29483008

DOI: doi.org/10.1016/j.jocn.2018.02.009

Titolo: The utilization of MGMT promoter methylation testing in United States hospitals for glioblastoma and its impact on prognosis.

Autori: Lee A., Youssef I., Osborn VW., Safdieh J., Becker DJ., Schreiber D.

Data di Pubblicazione: 2018-2-28

Abstract: Multiple studies have identified O

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 29442128

DOI: doi.org/10.1007/s00066-018-1276-4



Titolo: Semantic imaging features predict disease progression and survival in glioblastoma multiforme patients.

Autori: Peeken JC., Hesse J., Haller B., Kessel KA., Nüsslin F., Combs SE.

Data di Pubblicazione: 2018-2-15

Abstract: We demonstrated a predictive value of several qualitative imaging features for progression and survival. The performance of prognostic models was increased by combining clinical, pathological, and imaging features.

Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 29412012

DOI: doi.org/10.1080/10717544.2018.1436099

Titolo: Application of an assay Cascade methodology for a deep preclinical characterization of polymeric nanoparticles as a treatment for gliomas.

Autori: Fornaguera C., Lázaro MÁ., Brugada-Vilà P., Porcar I., Morera I., Guerra-Rebollo M., Garrido C., Rubio N., Blanco J., Cascante A., Borrós S.

Data di Pubblicazione: 2018-2-8

Abstract: Glioblastoma multiforme (GBM) is the most devastating primary brain tumor due to its infiltrating and diffuse growth characteristics, a situation compounded by the lack of effective treatments. Currently, many efforts are being devoted to find novel formulations to treat this disease, specifically in the nanomedicine field. However, due to the lack of comprehensive characterization that leads to insufficient data on reproducibility, only a reduced number of nanomedicines have reached clinical phases. In this context, the aim of the present study was to use a cascade of assays that evaluate from physical-chemical and structural properties to biological characteristics, both in vitro and in vivo, and also to check the performance of nanoparticles for glioma therapy. An amphiphilic block copolymer, composed of polyester and poly(ethylene glycol; PEG) blocks, has been synthesized. Using a mixture of this copolymer and a polymer containing an active targeting moiety to the Blood Brain Barrier (BBB; Seq12 peptide), biocompatible and biodegradable polymeric nanoparticles have been prepared and extensively characterized. In vitro studies demonstrated that nanoparticles are safe for normal cells but cytotoxic for cancer cells. In vivo studies in mice demonstrated the ability of the Seq12 peptide to cross the BBB. Finally, in vivo efficacy studies using a human tumor model in SCID mice resulted in a significant 50% life-span increase, as compared with non-treated animals. Altogether, this assay cascade provided extensive pre-clinical characterization of our polymeric nanoparticles, now ready for clinical evaluation.

Journal Title: Drug delivery

PUBMED ID: 29410102

DOI: doi.org/10.1016/j.wneu.2018.01.123

Titolo: Laser-Induced Thermal Therapy in Neuro-Oncology: A Review.

Autori: Ashraf O., Patel NV., Hanft S., Danish SF.

Data di Pubblicazione: 2018-2-8

Abstract: With the advent of real-time monitoring and damage estimation, LITT has gained ground in the management of intracranial tumors. Larger scale trials must be performed to develop standard protocols to define specific indications for use. Further large clinical studies for LITT in non-oncologic cases are also of interest.

Journal Title: World neurosurgery

PUBMED ID: 29396437

DOI: doi.org/10.1038/s41598-018-19825-w

Titolo: Gene therapy for human glioblastoma using neurotropic JC virus-like particles as a gene delivery vector.

Autori: Chao CN., Yang YH., Wu MS., Chou MC., Fang CY., Lin MC., Tai CK., Shen CH., Chen PL., Chang D., Wang M.

Data di Pubblicazione: 2018-2-4

Abstract: Glioblastoma multiforme (GBM), the most common malignant brain tumor, has a short period of survival even with recent multimodality treatment. The neurotropic JC polyomavirus (JCPyV) infects glial cells and oligodendrocytes and causes fatal progressive multifocal leukoencephalopathy in patients with AIDS. In this study, a possible gene therapy strategy for GBM using JCPyV virus-like particles (VLPs) as a gene delivery vector was investigated. We found that JCPyV VLPs were able to deliver the GFP reporter gene into tumor cells (U87-MG) for expression. In an orthotopic xenograft model, nude mice implanted with U87 cells expressing the near-infrared fluorescent protein and then treated by intratumoral injection of JCPyV VLPs carrying the thymidine kinase suicide gene, combined with ganciclovir administration, exhibited significantly prolonged survival and less tumor fluorescence during the experiment compared with controls. Furthermore, JCPyV VLPs were able to protect and deliver a suicide gene to distal subcutaneously implanted U87 cells in nude mice via blood circulation and inhibit tumor growth. These findings show that metastatic brain tumors can be targeted by JCPyV VLPs carrying a therapeutic gene, thus demonstrating the potential of JCPyV VLPs to serve as a gene therapy vector for the far highly treatment-refractory GBM.

Journal Title: Scientific reports

PUBMED ID: 29393706

DOI: doi.org/10.1080/07357907.2018.1430818

Titolo: Biomarkers in Recurrent Grade III Glioma Patients Treated with Bevacizumab and Irinotecan.

Autori: Toft A., Urup T., Christensen IJ., Michaelsen SR., Lukram B., Grunnet K., Kosteljanetz M., Larsen VA., Lassen U., Broholm H., Poulsen HS.

Data di Pubblicazione: 2018-2-3

Abstract: Predictive biomarkers and prognostic models are required to identify recurrent grade III glioma patients who benefit from existing treatment. In this study of 62 recurrent grade III glioma patients, a range of clinical and paraclinical factors are tested for association with progression-free survival, overall survival, and response to bevacizumab and irinotecan therapy. Significant factors from univariate screening are included in multivariate analysis. Biomarkers previously advanced as predictive or prognostic in the first-line setting did not affect outcome in this patient cohort. Based on the optimized model for overall survival, comprising performance status and p53 expression, a prognostic index is established.

Journal Title: Cancer investigation

PUBMED ID: 29392423

DOI: doi.org/10.1007/s00381-018-3739-4

Titolo: Marked functional recovery and imaging response of refractory optic pathway glioma to BRAFV600E inhibitor therapy: a report of two cases.

Autori: Upadhyaya SA., Robinson GW., Harreld JH., Klimo PD., Hoehn ME., Orr BA., Qaddoumi IA.

Data di Pubblicazione: 2018-2-3

Abstract: BRAFV600E inhibitor therapy can potentially reverse visual and neurologic decline associated with progressive OPG. The clinico-radiologic response appears to be prompt and marked. Ongoing clinical trials using BRAFV600E inhibitors can help confirm these early promising findings.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 29380489

DOI: doi.org/10.1002/hbm.23986

Titolo: Linking late cognitive outcome with glioma surgery location using resection cavity maps.

Autori: Hendriks EJ., Habets EJJ., Taphoorn MJB., Douw L., Zwinderman AH., Vandertop WP., Barkhof F., Klein M., De Witt Hamer PC.

Data di Pubblicazione: 2018-1-31

Abstract: Patients with a diffuse glioma may experience cognitive decline or improvement upon resective surgery. To examine the impact of glioma location, cognitive alteration after glioma surgery was quantified and related to voxel-based resection probability maps. A total of 59 consecutive patients (range 18-67 years of age) who had resective surgery between 2006 and 2011 for a supratentorial nonenhancing diffuse glioma (grade I-III, WHO 2007) were included in this observational cohort study. Standardized neuropsychological examination and MRI were obtained before and after surgery. Intraoperative stimulation mapping guided resections towards neurological functions (language, sensorimotor function, and visual fields). Maps of resected regions were constructed in standard space. These resection cavity maps were compared between patients with and without new cognitive deficits (z-score difference >1.5 SD between baseline and one year after resection), using a voxel-wise randomization test and calculation of false discovery rates. Brain regions significantly associated with cognitive decline were classified in standard cortical and subcortical anatomy. Cognitive improvement in any domain occurred in 10 (17%) patients, cognitive decline in any domain in 25 (42%), and decline in more than one domain in 10 (17%). The most frequently affected subdomains were attention in 10 (17%) patients and information processing speed in 9 (15%). Resection regions associated with decline in more than one domain were predominantly located in the right hemisphere. For attention decline, no specific region could be identified. For decline in information speed, several regions were found, including the frontal pole and the corpus callosum. Cognitive decline after resective surgery of diffuse glioma is prevalent, in particular, in patients with a tumor located in the right hemisphere without cognitive function mapping.

Journal Title: Human brain mapping

PUBMED ID: 29374809

DOI: doi.org/10.1007/s11060-018-2775-y

Titolo: Final results of a phase I dose-escalation, dose-expansion study of adding disulfiram with or without copper to adjuvant temozolomide for newly diagnosed glioblastoma.

Autori: Huang J., Campian JL., Gujar AD., Tsien C., Ansstas G., Tran DD., De Wees TA., Lockhart AC., Kim AH.

Data di Pubblicazione: 2018-1-29

Abstract: Disulfiram has shown promising activity including proteasome inhibitory properties and synergy with temozolomide in preclinical glioblastoma (GBM) models. In a phase I study for newly diagnosed GBM after chemoradiotherapy, we have previously reported our initial dose-escalation results combining disulfiram with adjuvant temozolomide and established the maximum tolerated dose (MTD) as 500 mg per day. Here we report the final results of the phase I study including an additional dose-expansion cohort of disulfiram with concurrent copper. The phase I study consisted of an initial dose-escalation phase of disulfiram 500-1000 mg daily during adjuvant temozolomide, followed by a dose-expansion phase of disulfiram 500 mg daily with copper 2 mg three times daily. Proteasome inhibition was assessed using fluorometric 20S proteasome assay on peripheral blood cell. A total of 18 patients were enrolled: 7 patients received 500 mg disulfiram, 5 patients received 1000 mg disulfiram, and 6 patients received 500 mg disulfiram with copper. Two dose-limiting toxicities occurred with 1000 mg disulfiram. At disulfiram 500 mg with or without copper, only 1 patient (7%) required dose-reduction during the first month of therapy. Addition of copper to disulfiram did not increase toxicity

nor proteasome inhibition. The median progression-free survival was 4.5 months (95% CI 0.8-8.2). The median overall survival (OS) was 14.0 months (95% CI 8.3-19.6), and the 2-year OS was 24%. The MTD of disulfiram at 500 mg daily in combination with adjuvant temozolomide was well tolerated by GBM patients, but 1000 mg daily was not. Toxicity and pharmacodynamic effect of disulfiram were similar with or without concurrent copper. The clinical efficacy appeared to be comparable to historical data. Additional clinical trials to combine disulfiram and copper with chemoradiotherapy or to resensitize recurrent GBM to temozolomide are ongoing.

Journal Title: Journal of neuro-oncology

PUBMED ID: 29374392

DOI: doi.org/10.1007/s13402-017-0361-5

Titolo: p53 expression and subcellular survivin localization improve the diagnosis and prognosis of patients with diffuse astrocytic tumors.

Autori: Faccion RS., Bernardo PS., de Lopes GPF., Bastos LS., Teixeira CL., de Oliveira JA., Fernandes PV., Dubois LG., Chimelli L., Maia RC.

Data di Pubblicazione: 2018-1-28

Abstract: Our data suggest that subcellular survivin localization and p53 expression may be employed as valuable tools to improve the accuracy of the histological sub-classification of diffuse astrocytic tumors. Patients whose tumors overexpress these proteins may benefit from radiotherapy, irrespective age and/or histological classification.

Journal Title: Cellular oncology (Dordrecht)

PUBMED ID: 29348883

DOI: doi.org/10.18632/oncotarget.22947

Titolo: Spatial habitats from multiparametric MR imaging are associated with signaling pathway activities and survival in glioblastoma.

Autori: Dextraze K., Saha A., Kim D., Narang S., Lehrer M., Rao A., Narang S., Rao D., Ahmed S., Madhugiri V., Fuller CD., Kim MM., Krishnan S., Rao G., Rao A.

Data di Pubblicazione: 2018-1-20

Abstract: Glioblastoma (GBM) show significant inter- and intra-tumoral heterogeneity, impacting response to treatment and overall survival time of 12-15 months. To study glioblastoma phenotypic heterogeneity, multi-parametric magnetic resonance images (MRI) of 85 glioblastoma patients from The Cancer Genome Atlas were analyzed to characterize tumor-derived spatial habitats for their relationship with outcome (overall survival) and to identify their molecular correlates (i.e., determine associated tumor signaling pathways correlated with imaging-derived habitat measurements). Tumor sub-regions based on four sequences (fluid attenuated inversion recovery, T1-weighted, post-contrast T1-weighted, and T2-weighted) were defined by automated segmentation. From relative intensity of pixels in the 3-dimensional tumor region, "imaging habitats" were identified and analyzed for their association to clinical and genetic data using survival modeling and Dirichlet regression, respectively. Sixteen distinct tumor sub-regions ("spatial imaging habitats") were derived, and those associated with overall survival (denoted "relevant" habitats) in glioblastoma patients were identified. Dirichlet regression implicated each relevant habitat with unique pathway alterations. Relevant habitats also had some pathways and cellular processes in common, including phosphorylation of STAT-1 and natural killer cell activity, consistent with cancer hallmarks. This work revealed clinical relevance of MRI-derived spatial habitats and their relationship with oncogenic molecular mechanisms in patients with GBM. Characterizing the associations between imaging-derived phenotypic measurements with the genomic and molecular characteristics of tumors can enable insights into tumor biology, further enabling the practice of personalized cancer

r treatment. The analytical framework and workflow demonstrated in this study are inherently scalable to multiple MR sequences.  
Journal Title: Oncotarget

PUBMED ID: 29340013

DOI: doi.org/10.18632/oncotarget.22500

Titolo: The small molecule SI113 synergizes with mitotic spindle poisons in arresting the growth of human glioblastoma multiforme.

Autori: Abbruzzese C., Catalogna G., Gallo E., di Martino S., Mileo AM., Carosi M., Dattilo V., Schenone S., Musumeci F., Lavia P., Perrotti N., Amato R., Paggi MG.

Data di Pubblicazione: 2018-1-18

Abstract: Glioblastoma multiforme (GBM) is the deadliest brain tumor. State-of-art GBM therapy often fails to ensure control of a disease characterized by high frequency of recurrences and progression. In search for novel therapeutic approaches, we assayed the effect of compounds from a cancer drug library on the ADF GBM cell line, establishing their elevated sensitivity to mitotic spindle poisons. Our previous work showed that the effectiveness of the spindle poison paclitaxel in inhibiting cancer cell growth was dependent on the expression of RANBP1, a regulatory target of the serine/threonine kinase SGK1. Recently, we developed the small molecule SI113 to inhibit SGK1 activity. Therefore, we explored the outcome of the association between SI113 and selected spindle poisons, finding that these drugs generated a synergistic cytotoxic effect in GBM cells, drastically reducing their viability and clonogenic capabilities

Journal Title: Oncotarget

PUBMED ID: 29339090

DOI: doi.org/10.1016/j.ajpath.2017.11.019

Titolo: Patched 1 Expression Correlates with Biochemical Relapse in High-Risk Prostate Cancer Patients.

Autori: Gonnissen A., Isebaert S., Perneel C., McKee CM., Van Utterbeeck F., Lerut E., Verrill C., Bryant RJ., Joniau S., Muschel RJ., Haustermans K.

Data di Pubblicazione: 2018-1-18

Abstract: There is an unmet clinical need for adequate biomarkers to aid risk stratification and management of prostate cancer (PCa) patients. Even within the high-risk PCa category, not all patients will invariably have a poor prognosis, and improved stratification of this heterogeneous group is needed. In this context, components of the hedgehog (Hh) pathway may have promise as biomarkers, because the available evidence suggests increased Hh pathway activity may confer a poorer outcome in advanced and castrate-resistant PCa. In this study, potential associations between Hh pathway protein expression and clinicopathological factors, including time to biochemical recurrence (BCR), were investigated using a tissue microarray constructed from benign and malignant prostate samples from 75 predominantly high-risk PCa patients who underwent radical prostatectomy. Hh signaling activity was found to differ between benign and malignant prostate tissue, with a greater amount of active Hh signaling present in malignant than benign prostate epithelium. High expression of Patched 1 in malignant prostate epithelium was found to be an independent predictor of BCR in high-risk PCa patients. Glioma-associated oncogene 1 may potentially represent a clinically useful biomarker of an aggressive tumor phenotype. Evaluation of Hh signaling activity in PCa patients may be useful for risk stratification, and epithelial Patched 1 expression, in particular, may be a prognostic marker for BCR in high-risk PCa patients.

Journal Title: The American journal of pathology

PUBMED ID: 29333019

DOI: doi.org/10.4103/ijmpo.ijmpo\_200\_16

Titolo: Modulated Radiotherapy with Concurrent and Adjuvant Temozolomide for Anaplastic Gliomas: Indian Single-center Data.

Autori: Kataria T., Basu T., Gupta D., Goyal S., Nasreen S., Bisht SS., Abhishek A., Banerjee S., Narang K., Jha AN., Mohapatra I., Modi JA.

Data di Pubblicazione: 2018-1-16

Abstract: Modulated RT with TMZ among Grade III glioma patients resulted in minimum treatment-related toxicities and encouraging survival. Molecular prognostic markers will determine most favorable groups in future.

Journal Title: Indian journal of medical and paediatric oncology : official journal of Indian Society of Medical & Paediatric Oncology

PUBMED ID: 29309981

DOI: doi.org/10.1016/j.wneu.2017.12.159

Titolo: Surgical Treatment of Spinal Ependymomas: Experience in 49 Patients.

Autori: Wild F., Hartmann C., Heissler HE., Hong B., Krauss JK., Nakamura M.

Data di Pubblicazione: 2018-1-9

Abstract: Gross total resection is considered the first choice in treatment of spinal ependymomas. The most important predictor of clinical outcome is postoperative neurologic functioning. The role of postoperative radiation needs further clarification.

Journal Title: World neurosurgery

PUBMED ID: 29308304

DOI: doi.org/10.1080/2162402X.2017.1382792

Titolo: PD-1 related transcriptome profile and clinical outcome in diffuse gliomas.

Autori: Liu S., Wang Z., Wang Y., Fan X., Zhang C., Ma W., Qiu X., Jiang T.

Data di Pubblicazione: 2018-1-9

Abstract: None

Journal Title: Oncoimmunology

PUBMED ID: 29294371

DOI: doi.org/10.1016/j.semcancer.2017.12.011

Titolo: Targeting the Warburg effect for cancer treatment: Ketogenic diets for or management of glioma.

Autori: Poff A., Koutnik AP., Egan KM., Sahebjam S., D'Agostino D., Kumar NB.

Data di Pubblicazione: 2018-1-3

Abstract: Gliomas are a highly heterogeneous tumor, refractory to treatment and the most frequently diagnosed primary brain tumor. Although the current WHO grading system (2016) demonstrates promise towards identifying novel treatment modalities and better prediction of prognosis over time, to date, existing targeted and monotherapy approaches have failed to elicit a robust impact on disease progression and patient survival. It is possible that tumor heterogeneity as well as specifically targeted agents fail because redundant molecular pathways in the tumor make it refractory to such approaches. Additionally, the underlying metabolic pathology, which is significantly altered during neoplastic transformation and tumor progression, is unaccounted for. With several molecular and metabolic pathways implicated in the carcinogenesis of CNS tumors, including glioma, we postulate that a systemic, broad spectrum approach to produce robust targeting of relevant and multiple molecular and metabolic regulation of growth and survival pathways, critical to the modulation of hallmarks of carcinogenesis, without clinically limiting toxicity, may provide a more sustained impact on clinical outcomes compared to the modalities of treatment evaluated to date. The objective of this review is to examine the emerging hallmark of reprogramming energy metabolism of the tu

mor cells and the tumor microenvironment during carcinogenesis, and to provide a rationale for exploiting this hallmark and its biological capabilities as a target for secondary chemoprevention and treatment of glioma. This review will primarily focus on interventions to induce ketosis to target the glycolytic phenotype of many cancers, with specific application to secondary chemoprevention of low grade glioma- to halt the progression of lower grade tumors to more aggressive subtypes, as evidenced by reduction in validated intermediate endpoints of disease progression including clinical symptoms.

Journal Title: Seminars in cancer biology

PUBMED ID: 29291003

DOI: doi.org/10.18632/oncotarget.22197

Titolo: Pseudogenes of annexin A2, novel prognosis biomarkers for diffuse gliomas.

Autori: Li S., Zou H., Shao YY., Mei Y., Cheng Y., Hu DL., Tan ZR., Zhou HH.

Data di Pubblicazione: 2018-1-2

Abstract: Diffuse gliomas is a kind of common malignant primary brain tumor. Pseudogenes have multilayered biological function in the progression of human cancers. In this study, Differentially Expressed Pseudogenes (DEPs) between glioblastomas and non-tumor controls were found by bioinformatics analysis, of which the annexin A2 pseudogenes (ANXA2P1, ANXA2P2 and ANXA2P3) were significantly up-regulated, along with the parent gene annexin A2 (ANXA2

Journal Title: Oncotarget

PUBMED ID: 29260361

DOI: doi.org/10.1007/s11060-017-2714-3

Titolo: Sex-dependent association of preoperative hematologic markers with glioma grade and progression.

Autori: Xu W., Wang D., Zheng X., Ou Q., Huang L.

Data di Pubblicazione: 2017-12-21

Abstract: Neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio, the systemic immune-inflammation index (SII), and red blood cell distribution width (RDW), have been recognized as promising predictors for histological grade and prognosis in multiple cancer types. However, few investigations illustrated the impacts of sex on the clinical utility of hematologic markers. Patients with primary gliomas were retrospectively reviewed. The association between grade and inflammatory markers by sex were investigated by univariate and multivariate analysis. The discrimination ability of logistic regression model was evaluated by the area under the receiver-operating characteristic curve (AUC) for high-grade glioma (HGG). Kaplan-Meier progression-free survival (PFS) curves were plotted to assess the prognostic value of RDW. In subgroup analysis, distinctively elevated NLR and SII levels were exclusively present in male HGGs group ( $p=0.001$ ); whereas RDW notably increased in female HGGs group ( $p=0.001$ ). On multivariate analysis, increased odds ratio of HGGs was exclusively observed for female patients with elevated RDW (odds ratio=1.589). Moreover, regression model developed by RDW exhibited an excellent discriminative ability for the prediction of HGGs in female patients (AUC=0.817). Median progression time with RDW<13.2 versus RDW≥13.2 was 62.5 versus 33.0 months (log rank  $p=0.017$ ). Older females (≥45 years) with increased RDW levels portended worse survival (HR 3.693, 95% CI 1.747-8.325,  $p=0.001$ ). Meanwhile, the significant association of RDW levels with PFS in male subgroup was not observed ( $p>0.05$ ). In conclusion, superior to NLR and SII, RDW would be sex-specific predictor for tumor grade and progression for HGG female patients.

Journal Title: Journal of neuro-oncology

PUBMED ID: 29258767

DOI: doi.org/10.1016/j.prp.2017.12.009

Titolo: Immunohistochemical comparative analysis of GFAP, MAP - 2, NOGO - A, OLIG - 2 and WT - 1 expression in WHO 2016 classified neuroepithelial tumours and their prognostic value.

Autori: Schwab DE., Lepski G., Borchers C., Trautmann K., Paulsen F., Schittenhelm J.

Data di Pubblicazione: 2017-12-21

Abstract: Immunohistochemistry is routinely used in differential diagnosis of tumours of the central nervous system (CNS). The latest 2016 WHO 2016 revision now includes molecular data such as IDH mutation and 1p/19q codeletion thus restructuring glioma classification. Direct comparative information between commonly used immunohistochemical markers for glial tumours GFAP, MAP - 2, NOGO - A, OLIG - 2 and WT - 1 concerning quality and quantity of expression and their relation to the new molecular markers are lacking. We therefore compared the immunohistochemical staining results of all five antibodies in 34 oligodendrogliomas, 106 ependymomas and 423 astrocytic tumours. GFAP expression was reduced in cases with higher WHO grade, oligodendroglial differentiation and in IDH wildtype diffuse astrocytomas. By contrast MAP - 2 expression was significantly increased in diffuse astrocytomas with IDH mutation, while NOGO - A expression was not associated with any molecular marker. WT - 1 expression was significantly decreased in tumours with IDH mutation and ATRX loss. OLIG - 2 was increased in IDH-mutant grade II astrocytomas and in cases with higher proliferation rate. In univariate survival analysis high WT - 1 expression was significantly associated with worse outcome in diffuse astrocytic tumours (log rank  $p < 0.0001$ ;  $n = 211$ ; median time: 280 days vs 562 days). None of the markers was prognostic in multivariate survival analysis. Among the evaluated markers MAP - 2, OLIG - 2 and WT - 1 showed the best potential to separate between glioma entities and can be recommended for a standardized immunohistochemical panel.

Journal Title: Pathology, research and practice

PUBMED ID: 29254497

DOI: doi.org/10.1186/s40425-017-0302-x

Titolo: Retrospective review of safety and efficacy of programmed cell death -1 inhibitors in refractory high grade gliomas.

Autori: Reiss SN., Yerram P., Modelevsky L., Grommes C.

Data di Pubblicazione: 2017-12-20

Abstract: While response rates are low, a few patients had a prolonged PFS. Pembrolizumab was tolerated with few serious toxicities, even in patients receiving concomitant therapy.

Journal Title: Journal for immunotherapy of cancer

PUBMED ID: 29250697

DOI: Mancante

Titolo: Two girl patients with medulloblastoma. Case reports.

Autori: Marinău LD., Singer CE., Meșină C., Niculescu EC., Puiu I., Petrescu IO., Geormăneanu C., Enculescu AC., Tache DE., Purcaru ȘO., Răciulă S., Damian CL.

Data di Pubblicazione: 2017-12-19

Abstract: As medulloblastoma is a very aggressive malignant tumor, the approximate cumulative survival rate for preschool age group having a histological follow-up was found to be 47% over a span of five years of rigorous treatment.

Journal Title: Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie



PUBMED ID: 29245310  
DOI: doi.org/10.1097/MD.00000000000009053  
Titolo: A pilot clinical study of apatinib plus irinotecan in patients with recurrent high-grade glioma: Clinical Trial/Experimental Study.  
Autori: Wang L., Liang L., Yang T., Qiao Y., Xia Y., Liu L., Li C., Lu P., Jiang X.  
Data di Pubblicazione: 2017-12-17  
Abstract: NCT02848794/Ahead-BG306.  
Journal Title: Medicine

PUBMED ID: 29239262  
DOI: doi.org/10.1080/0284186X.2017.1413248  
Titolo: Outcomes following proton therapy for pediatric ependymoma.  
Autori: Indelicato DJ., Bradley JA., Rotondo RL., Nanda RH., Logie N., Sandler ES., Aldana PR., Ranalli NJ., Beier AD., Morris CG., Mendenhall NP.  
Data di Pubblicazione: 2017-12-15  
Abstract: This series of proton therapy for pediatric intracranial ependymoma demonstrates disease control comparable to photon series without unexpected toxicity. Subtotal resection and male sex were associated with inferior disease control. Additional follow-up to quantify the expected reductions in late toxicity with proton therapy is ongoing.  
Journal Title: Acta oncologica (Stockholm, Sweden)

PUBMED ID: 29229328  
DOI: doi.org/10.1016/j.ijrobp.2017.10.002  
Titolo: Outcomes After Reirradiation for Recurrent Pediatric Intracranial Ependymoma.  
Autori: Tsang DS., Burghen E., Klimo P., Boop FA., Ellison DW., Merchant TE.  
Data di Pubblicazione: 2017-12-13  
Abstract: Reirradiation for relapsed pediatric ependymoma was well tolerated by most patients and resulted in long-term survival in a subset of patients. The best results were observed in patients who experienced distant-only failure after RT1 and were treated with CSI as part of RT2, without anaplasia at recurrence. The option of reirradiation should be discussed with patients who develop recurrent ependymoma.  
Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 29218626  
DOI: doi.org/10.1007/s12094-017-1816-x  
Titolo: Treatment-related changes in glioblastoma: a review on the controversies in response assessment criteria and the concepts of true progression, pseudoprogression, pseudoresponse and radionecrosis.  
Autori: Delgado-López PD., Riñones-Mena E., Corrales-García EM.  
Data di Pubblicazione: 2017-12-9  
Abstract: The assessment of response to therapy in glioblastoma remains a challenge, because the surrogate measures of survival are subject to radiographic misinterpretation. A solid and reliable definition of progression is needed for both clinical decision-making and for evaluating response within the clinical trials. Historically, assessment criteria have used radiologic and clinical features aimed to correctly classify patients into progressive or non-progressive disease. The widely used RANO criteria are a valuable tool in disease evaluation, both in the clinical setting and in the clinical trials. However, assessment criteria have certain limitations that emerging techniques have tried to overcome. Differentiating true progression from treatment-related changes (like pseudoprogression or pseudoresponse) is crucial i

n order not to prematurely discontinue adjuvant chemotherapy or redirect the patient to second-line options. This fact underscores the need for advanced radiologic techniques, like specific diffusion and perfusion MRI sequences, MR spectroscopy and PET, which seem to play a role in distinguishing these phenomena.

Journal Title: Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico

PUBMED ID: 29207176

DOI: doi.org/10.3892/or.2017.6134

Titolo: P4HB and PDIA3 are associated with tumor progression and therapeutic outcome of diffuse gliomas.

Autori: Zou H., Wen C., Peng Z., Shao YY., Hu L., Li S., Li C., Zhou HH.

Data di Pubblicazione: 2017-12-6

Abstract: Diffuse gliomas are the most common type of primary brain and central nervous system (CNS) tumors. Protein disulfide isomerases (PDIs) such as P4HB and PDIA3 act as molecular chaperones for reconstructing misfolded proteins, and are involved in endoplasmic reticulum stress and the unfolded protein response. The present study focused on the role of P4HB and PDIA3 in diffuse gliomas. Analysis of GEO and HPA data revealed that the expression levels of P4HB and PDIA3 were upregulated in glioma datasets. their increased expression was then validated in 99 glioma specimens compared with 11 non-tumor tissues. High expression of P4HB and PDIA3 was significantly correlated with high Ki-67 and a high frequency of the TP53 mutation. Kaplan-Meier survival curve and Cox regression analyses showed that glioma patients with high P4HB and PDIA3 expression had a poor survival outcome, P4HB and PDIA3 could be independent prognostic biomarkers for diffuse gliomas. In vitro, knockdown of PDIA3 suppressed cell proliferation, induced cell apoptosis, and decreased the migration of glioma cells. Furthermore, downregulation of P4HB and PDIA3 may contribute to improve the survival of patients who receive chemotherapy and radiotherapy. The data suggest that high expression of P4HB and PDIA3 plays an important role in glioma progression, and could predict the survival outcome and therapeutic response of glioma patients. Therefore, protein disulfide isomerases may be explored as prognostic biomarkers and therapeutic targets for diffuse gliomas.

Journal Title: Oncology reports

PUBMED ID: 29198053

DOI: doi.org/10.1007/s11060-017-2702-7

Titolo: Diffuse intrinsic pontine gliomas (DIPG) at recurrence: is there a window to test new therapies in some patients?

Autori: Lobon-Iglesias MJ., Giraud G., Castel D., Philippe C., Debily MA., Briandet C., Fouyssac F., de Carli E., Dufour C., Valteau-Couanet D., Sainte-Rose C., Blauwblomme T., Beccaria K., Zerah M., Puget S., Calmon R., Boddaert N., Bolle S., Varlet P., Grill J.

Data di Pubblicazione: 2017-12-4

Abstract: Children with diffuse intrinsic pontine glioma (DIPG) need new and more efficient treatments. They can be developed at relapse or at diagnosis, but therefore they must be combined with radiotherapy. Survival of children after recurrence and its predictors were studied to inform the possibility to design early phase clinical trials for DIPG at this stage. Among 142 DIPG patients treated between 1998 and 2014, 114 had biopsy-proven DIPG with histone H3 status available for 83. We defined as long survivors' patients who survived more than 3 months after relapse which corresponds to the minimal life expectancy requested for phase I/II trials. Factors influencing post-relapse survival were accordingly compared between short and long-term survivors after relapse. Fifty-seven percent of patients were considered long survivor

s and 70% of them had a Lansky Play Scale (LPS) above 50% at relapse. Patients who became steroids-independent after initial treatment for at least 2 months had better survival after relapse (3.7 versus 2.6 months,  $p=0.001$ ). LPS above 50% at relapse was correlated with better survival after relapse (3.8 versus 1.8 months,  $p<0.001$ ). Patients with H3.1 mutation survived longer after relapse (4.9 versus 2.7 months,  $p=0.007$ ). Patients who received a second radiotherapy at the time of relapse had an improved survival (7.5 versus 4 months,  $p=0.001$ ). In the two-way ANOVA analysis, steroid-independence and LPS predicted survival best and the type of histone H3 (H3.1 or H3.3) mutated did not improve prediction. Survival of many DIPG patients after relapse over 3 months would make possible to propose specific trials for this condition. Steroid-independence, H3 mutation status and LPS should be considered to predict eligibility.

Journal Title: Journal of neuro-oncology

PUBMED ID: 29195506

DOI: doi.org/10.1186/s13014-017-0924-7

Titolo: Treatment of meningioma and glioma with protons and carbon ions.

Autori: Adeberg S., Harrabi SB., Verma V., Bernhardt D., Grau N., Debus J., Rieken S.

Data di Pubblicazione: 2017-12-3

Abstract: The rapid rise of particle therapy across the world necessitates evidence to justify its ever-increasing utilization. This narrative review summarizes the current status of these technologies on treatment of both meningiomas and gliomas, the most common benign and malignant primary brain tumors, respectively. Proton beam therapy (PBT) for meningiomas displays high rates of long-term local control, low rates of symptomatic deterioration, along with the potential for safe dose-escalation in select (but not necessarily routine) cases. PBT is also associated with low adverse events and maintenance of functional outcomes, which have implications for quality of life and cost-effectiveness measures going forward. Data on carbon ion radiation therapy (CIRT) are limited; existing series describe virtually no high-grade toxicities and high local control. Regarding the few available data on low-grade gliomas, PBT provides opportunities to dose-escalate while affording no increase of severe toxicities, along with maintaining appropriate quality of life. Although dose-escalation for low-grade disease has been less frequently performed than for glioblastoma, PBT and CIRT continue to be utilized for the latter, and also have potential for safer re-irradiation of high-grade gliomas. For both neoplasms, the impact of superior dosimetric profiles with endpoints such as neurocognitive decline and neurologic functionality, are also discussed to the extent of requiring more data to support the utility of particle therapy. Caveats to these data are also described, such as the largely retrospective nature of the available studies, patient selection, and heterogeneity in patient population as well as treatment (including mixed photon/particle treatment). Nevertheless, multiple prospective trials (which may partially attenuate those concerns) are also discussed. In light of the low quantity and quality of available data, major questions remain regarding economic concerns as well.

Journal Title: Radiation oncology (London, England)

PUBMED ID: 29192869

DOI: doi.org/10.3171/2017.7.PEDS17133

Titolo: Predictors of clinical outcome in pediatric oligodendroglioma: meta-analysis of individual patient data and multiple imputation.

Autori: Wang KY., Vankov ER., Lin DDM.

Data di Pubblicazione: 2017-12-2

**Abstract:** **OBJECTIVE** Oligodendroglioma is a rare primary CNS neoplasm in the pediatric population, and only a limited number of studies in the literature have characterized this entity. Existing studies are limited by small sample sizes and discrepant interstudy findings in identified prognostic factors. In the present study, the authors aimed to increase the statistical power in evaluating for potential prognostic factors of pediatric oligodendrogliomas and sought to reconcile the discrepant findings present among existing studies by performing an individual-patient-data (IPD) meta-analysis and using multiple imputation to address data not directly available from existing studies. **METHODS** A systematic search was performed, and all studies found to be related to pediatric oligodendrogliomas and associated outcomes were screened for inclusion. Each study was searched for specific demographic and clinical characteristics of each patient and the duration of event-free survival (EFS) and overall survival (OS). Given that certain demographic and clinical information of each patient was not available within all studies, a multivariable imputation via chained equations model was used to impute missing data after the mechanism of missing data was determined. The primary end points of interest were hazard ratios for EFS and OS, as calculated by the Cox proportional-hazards model. Both univariate and multivariate analyses were performed. The multivariate model was adjusted for age, sex, tumor grade, mixed pathologies, extent of resection, chemotherapy, radiation therapy, tumor location, and initial presentation. A p value of less than 0.05 was considered statistically significant. **RESULTS** A systematic search identified 24 studies with both time-to-event and IPD characteristics available, and a total of 237 individual cases were available for analysis. A median of 19.4% of the values among clinical, demographic, and outcome variables in the compiled 237 cases were missing. Multivariate Cox regression analysis revealed subtotal resection ( $p = 0.007$  [EFS] and  $0.043$  [OS]), initial presentation of headache ( $p = 0.006$  [EFS] and  $0.004$  [OS]), mixed pathologies ( $p = 0.005$  [EFS] and  $0.049$  [OS]), and location of the tumor in the parietal lobe ( $p = 0.044$  [EFS] and  $0.030$  [OS]) to be significant predictors of tumor progression or recurrence and death. **CONCLUSIONS** The use of IPD meta-analysis provides a valuable means for increasing statistical power in investigations of disease entities with a very low incidence. Missing data are common in research, and multiple imputation is a flexible and valid approach for addressing this issue, when it is used conscientiously. Undergoing subtotal resection, having a parietal tumor, having tumors with mixed pathologies, and suffering headaches at the time of diagnosis portended a poorer prognosis in pediatric patients with oligodendroglioma.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 29179732

DOI: doi.org/10.1186/s13046-017-0642-x

Titolo: Drug repurposing for the treatment of glioblastoma multiforme.

Autori: Abbruzzese C., Matteoni S., Signore M., Cardone L., Nath K., Glickson JD., Paggi MG.

Data di Pubblicazione: 2017-11-29

**Abstract:** The spiraling costs of new antineoplastic drugs and the long time required for them to reach the market demands a profoundly different approach to keep lifesaving therapies affordable for cancer patients. In this context, repurposing can represent a relatively inexpensive, safe and fast approach to glioblastoma treatment. To this end, pros and cons must be accurately considered.

Journal Title: Journal of experimental & clinical cancer research : CR

PUBMED ID: 29166609

DOI: doi.org/10.1016/j.celrep.2017.10.083

Titolo: GPR56/ADGRG1 Inhibits Mesenchymal Differentiation and Radioresistance in Glioblastoma.

Autori: Moreno M., Pedrosa L., Paré L., Pineda E., Bejarano L., Martínez J., Balasubramaniyan V., Ezhilarasan R., Kallarackal N., Kim SH., Wang J., Audia A., Conroy S., Marin M., Ribalta T., Pujol T., Herreros A., Tortosa A., Mira H., Alonso MM., Gómez-Manzano C., Graus F., Sulman EP., Piao X., Nakano I., Prat A., Bhat KP., de la Iglesia N.

Data di Pubblicazione: 2017-11-23

Abstract: A mesenchymal transition occurs both during the natural evolution of glioblastoma (GBM) and in response to therapy. Here, we report that the adhesion G-protein-coupled receptor, GPR56/ADGRG1, inhibits GBM mesenchymal differentiation and radioresistance. GPR56 is enriched in proneural and classical GBMs and is lost during their transition toward a mesenchymal subtype. GPR56 loss of function promotes mesenchymal differentiation and radioresistance of glioma initiating cells both in vitro and in vivo. Accordingly, a low GPR56-associated signature is prognostic of a poor outcome in GBM patients even within non-G-CIMP GBMs. Mechanistically, we reveal GPR56 as an inhibitor of the nuclear factor kappa B (NF- $\kappa$ B) signaling pathway, thereby providing the rationale by which this receptor prevents mesenchymal differentiation and radioresistance. A pan-cancer analysis suggests that GPR56 might be an inhibitor of the mesenchymal transition across multiple tumor types beyond GBM.

Journal Title: Cell reports

PUBMED ID: 29150792

DOI: doi.org/10.1007/s12020-017-1474-3

Titolo: Correlation between MGMT promoter methylation and response to temozolomide-based therapy in neuroendocrine neoplasms: an observational retrospective multicenter study.

Autori: Campana D., Walter T., Pusceddu S., Gelsomino F., Graillot E., Prinzi N., Spallanzani A., Fiorentino M., Barritault M., Dall'Olio F., Brighi N., Biasco G.

Data di Pubblicazione: 2017-11-19

Abstract: According to our results, MGMT methylation status, evaluated with methylation specific-polymerase chain reaction or pyrosequencing, should have an important role in patients with metastatic NENs, in order to guide therapeutic options. These results need further confirmation with prospective studies.

Journal Title: Endocrine

PUBMED ID: 29143923

DOI: doi.org/10.1007/s11060-017-2668-5

Titolo: Impact of concurrent versus adjuvant chemotherapy on the severity and duration of lymphopenia in glioma patients treated with radiation therapy.

Autori: Lin AJ., Campian JL., Hui C., Rudra S., Rao YJ., Thotala D., Hallahan D., Huang J.

Data di Pubblicazione: 2017-11-17

Abstract: Prolonged severe lymphopenia has been shown to persist beyond a year in glioma patients after radiation therapy (RT) with concurrent and adjuvant chemotherapy. This study examines the differential impact of concurrent versus adjuvant chemotherapy on lymphopenia after RT. WHO grade II-III glioma patients who received RT with concurrent and/or adjuvant chemotherapy from 2007 to 2016 were retrospectively analyzed. Concurrent chemotherapy was temozolomide (TMZ), and adjuvant chemotherapy was either TMZ or procarbazine/lomustine/vincristine (PCV). Absolute lymphocyte count (ALC) was analyzed at baseline, 1.5, 3, 6, and 12 months after the start of RT. Univariable and multivariable logistic regression were used to identify the clinical variables in predicting acute or late lymphopenia. There were 151 patients with evaluab

le ALC: 91 received concurrent and adjuvant TMZ (CRT+ADJ), 32 received only concurrent TMZ (CRT), and 28 received only adjuvant TMZ or PCV (ADJ). There were 9 (10%) versus 6 (19%) versus 0 (0%) cases of grade 3 lymphopenia (ALC < 500/mm

Journal Title: Journal of neuro-oncology

PUBMED ID: 29125440

DOI: doi.org/10.3171/2017.7.PEDS17168

Titolo: Long-term outcomes of primarily metastatic juvenile pilocytic astrocytoma in children.

Autori: Yecies D., Fisher PG., Cheshier S., Edwards M., Grant G.

Data di Pubblicazione: 2017-11-11

Abstract: OBJECTIVE Primarily metastatic juvenile pilocytic astrocytoma (JPA) is rare, likely representing 2%-3% of all cases of JPA. Due to the rarity of primarily metastatic JPA, there is currently no standard treatment paradigm and the long-term outcomes are not fully known. The goal of this case series was to add to the current understanding of this disease process. METHODS The authors searched a comprehensive database of pediatric patients with brain and spinal cord tumors treated at Lucile Packard Children's Hospital from 1997 to 2016 and identified 5 patients with primarily metastatic JPA. A retrospective chart review was performed and details of the patients' treatment and clinical course were recorded for further analysis. RESULTS For the 5 patients with primarily metastatic JPA, the mean follow-up period was 12.3 years. All patients in our series had biopsies or subtotal resections and upfront treatment. Three patients were treated with chemotherapy alone, one was treated with chemotherapy and radiotherapy, and one was treated with radiotherapy alone. Four patients had stable disease after initial treatment, and one patient had multiple episodes of progressive disease but underwent successful salvage therapy and has had stable disease for 19 years. One patient died of an intracerebral hemorrhage 10 years following initial radiation treatment believed to be secondary to radiation vasculopathy. CONCLUSIONS Evaluation of the entire neuraxis should be performed in all instances of initial JPA diagnosis to properly assess for primarily metastatic disease. Many patients with primarily metastatic JPA will have stable disease after upfront treatment, although the higher rate of stable disease found in this series relative to other reports is likely secondary to the small sample size.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 29118304

DOI: doi.org/10.2176/nmc.ra.2017-0081

Titolo: Pediatric Optic Pathway/Hypothalamic Glioma.

Autori: Aihara Y., Chiba K., Eguchi S., Amano K., Kawamata T.

Data di Pubblicazione: 2017-11-10

Abstract: Optic pathway/hypothalamic gliomas (OP/HGs) are rare astrocytic tumors that appear more commonly among young children and often are unresectable. They comprise approximately 2% of all central nervous system tumors and account for 3-5% of pediatric intracranial tumors. Initial manifestations are often visual disturbances, endocrinopathies and hypothalamic dysfunction such as the diencephalic syndrome, and sometimes hydrocephalus due to cerebrospinal fluid (CSF) outflow obstruction. In many cases, the tumors are diagnosed late in the clinical course because they silently enlarge. These tumors consist mostly of histologically benign, World Health Organization (WHO) grade I tumors represented by pilocytic astrocytomas (PA), the rest being pilomyxoid astrocytomas (PXA) - WHO grade II tumors. In young pediatric patients, however, can be seen PXA that show aggressive clinical course such as CSF dissemination. Our small series of 14 non-Neurofibromatosis type 1 (NF-1) OP/HGs PA patients underwent extended resection without any adjuvant treatments.

The median age at initial treatment was  $11.5 \pm 6.90$  years (range, 1-25 years) and median follow up  $85.5 \pm 25.0$  months. Surgical resection for OP/HGs results in acceptable middle-term survival, tumor control and functional outcome equivalent to chemotherapy. There is, however, no longer doubt that chemotherapy with or without biopsy and as-needed debulking surgery remains the golden standard in management of OP/H. Clinical conditions and treatment plans for OP/HGs vary depending on their structure of origin.

Journal Title: Neurologia medico-chirurgica

PUBMED ID: 29113369

DOI: doi.org/10.18632/oncotarget.19080

Titolo: Prognostic role of Gli1 expression in breast cancer: a meta-analysis

Autori: Wang B., Yu T., Hu Y., Xiang M., Peng H., Lin Y., Han L., Zhang L.

Data di Pubblicazione: 2017-11-9

Abstract: Glioma-associated oncogene 1 (Gli1) is a critical transcriptional factor of Sonic hedgehog pathway which has been proved to participate in the initiation and progression of tumor in mammals. However, its clinical value in breast cancer remains unknown. Thus, a meta-analysis was performed to clarify the association of Gli1 over-expression, clinic-pathological characteristics, molecular subtypes and prognosis in breast cancer. According to included criteria, 13 eligible studies containing 2816 patients all around the world were selected in this study. Our results indicated no significant association of Gli1 expression and histological grade (RR = 1.20, 95% CI: [0.98, 1.47]), T stage (RR = 1.05, 95% CI: [0.87, 1.27]), clinical stage (RR = 1.04, 95% CI: [0.93, 1.18]) and lymph node metastasis (RR = 1.12, 95% CI: [0.92, 1.37]). In addition, pooled RR showed no correlation of Gli1 expression and progesterone receptor (PR) (RR = 0.92, 95% CI: [0.70, 1.21]), estrogen receptor (ER) (RR = 1.03, 95% CI: [0.74, 1.42]), human epidermal growth factor receptor 2 (HER-2) (RR = 1.12, 95% CI: [0.90, 1.39]). Nonetheless, up-regulated Gli1 expression predicts shorter disease-free survival (DFS) (HR = 1.38, 95% CI: [1.05, 1.81]), 3-year survival (HR = 1.74, 95% CI: [1.28, 2.36]), 5-year survival (HR = 2.04, 95% CI: [1.62, 2.57]) and overall survival (OS) (HR = 2.05, 95% CI: [1.60, 2.64]). In conclusion, over-expression of Gli1 tends to progressive stages and is related to unfavorable prognosis of breast cancer, which may become a potential prognosis indicator and therapy target in breast cancer.

Journal Title: Oncotarget

PUBMED ID: 29108264

DOI: doi.org/10.18632/oncotarget.20226

Titolo: lncRNAs PVT1 and HAR1A are prognosis biomarkers and indicate therapy outcome for diffuse glioma patients.

Autori: Zou H., Wu LX., Yang Y., Li S., Mei Y., Liu YB., Zhang L., Cheng Y., Zhou HH.

Data di Pubblicazione: 2017-11-8

Abstract: Diffuse gliomas are well known malignant brain tumors. Long non-coding RNAs (lncRNAs), a type of RNA transcript with more than 200 nucleotides, involve in tumorigenesis and development of various cancers. This study focused on identifying differentially expressed lncRNAs in gliomas based on gene expression profiling, and chose certain lncRNAs PVT1, CYTOR, HAR1A and MIAT, which changed with significant differences. Further analysis of TCGA and GEO data revealed that the expressions of PVT1 and CYTOR were up-regulated, while HAR1A and MIAT expressions were down-regulated in gliomas. Their expression patterns were validated in an independent cohort containing 98 glioma specimens and 12 non-tumor tissue controls. High expression of PVT1 and CYTOR as well as low HAR1A and MIAT expression were associated with high Ki-67 level and more

Journal Title: Oncotarget

PUBMED ID: 29093005

DOI: doi.org/10.1158/0008-5472.CAN-17-0469

Titolo: Dendritic Cells Enhance Polyfunctionality of Adoptively Transferred T Cells That Target Cytomegalovirus in Glioblastoma.

Autori: Reap EA., Suryadevara CM., Batich KA., Sanchez-Perez L., Archer GE., Schmittling RJ., Norberg PK., Herndon JE., Healy P., Congdon KL., Gedeon PC., Campbell OC., Swartz AM., Riccione KA., Yi JS., Hossain-Ibrahim MK., Saraswathula A., Nair SK., Dunn-Pirio AM., Broome TM., Weinhold KJ., Desjardins A., Vlahovic G., McLendon RE., Friedman AH., Friedman HS., Bigner DD., Fecci PE., Mitchell DA., Sampson JH.

Data di Pubblicazione: 2017-11-3

Abstract: Median survival for glioblastoma (GBM) remains <15 months. Human cytomegalovirus (CMV) antigens have been identified in GBM but not normal brain, providing an unparalleled opportunity to subvert CMV antigens as tumor-specific immunotherapy targets. A recent trial in recurrent GBM patients demonstrated the potential clinical benefit of adoptive T-cell therapy (ATCT) of CMV phosphoprotein 65 (pp65)-specific T cells. However,

Journal Title: Cancer research

PUBMED ID: 29090526

DOI: doi.org/10.1002/pbc.26832

Titolo: A pediatric brain tumor consortium phase II trial of capecitabine rapidly disintegrating tablets with concomitant radiation therapy in children with newly diagnosed diffuse intrinsic pontine gliomas.

Autori: Kilburn LB., Kocak M., Baxter P., Poussaint TY., Paulino AC., McIntyre C., Lemenue-Diot A., Lopez-Diaz C., Kun L., Chintagumpala M., Su JM., Broniscer A., Baker JN., Hwang EI., Fouladi M., Boyett JM., Blaney SM.

Data di Pubblicazione: 2017-11-2

Abstract: Capecitabine did not improve the outcome for children with newly diagnosed DIPG.

Journal Title: Pediatric blood & cancer

PUBMED ID: 29076150

DOI: doi.org/10.1111/bjh.14987

Titolo: A phase 1 clinical trial evaluating marizomib, pomalidomide and low-dose dexamethasone in relapsed and refractory multiple myeloma (NPI-0052-107): final study results.

Autori: Spencer A., Harrison S., Zonder J., Badros A., Laubach J., Bergin K., Khot A., Zimmerman T., Chauhan D., Levin N., MacLaren A., Reich SD., Trikhama M., Richardson P.

Data di Pubblicazione: 2017-10-28

Abstract: Marizomib (MRZ) is an irreversible, pan-subunit proteasome inhibitor (PI) in clinical development for relapsed/refractory multiple myeloma (RRMM) and glioma. This study analysed MRZ, pomalidomide (POM) and low-dose dexamethasone (Lo-DEX) [PMD] in RRMM to evaluate safety and determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D). Intravenous MRZ (0.3-0.5 mg/m

Journal Title: British journal of haematology

PUBMED ID: 29076027

DOI: doi.org/10.1007/s13402-017-0355-3

Titolo: Serum exosomal miR-301a as a potential diagnostic and prognostic biomarker for human glioma.

Autori: Lan F., Qing Q., Pan Q., Hu M., Yu H., Yue X.



Data di Pubblicazione: 2017-10-28

Abstract: Our data indicate that serum exosomal miR-301a levels may reflect the cancer-bearing status and pathological changes in glioma patients. Serum exosomal miR-301a expression may serve as a novel biomarker for glioma diagnosis and as a prognostic factor for advanced grade disease.

Journal Title: Cellular oncology (Dordrecht)

PUBMED ID: 29074604

DOI: doi.org/10.1158/1078-0432.CCR-17-0963

Titolo: Prospective Feasibility Trial for Genomics-Informed Treatment in Recurrent and Progressive Glioblastoma.

Autori: Byron SA., Tran NL., Halperin RF., Phillips JJ., Kuhn JG., de Groot JF., Colman H., Ligon KL., Wen PY., Cloughesy TF., Mellinghoff IK., Butowski NA., Taylor JW., Clarke JL., Chang SM., Berger MS., Molinaro AM., Maggiora G M., Peng S., Nasser S., Liang WS., Trent JM., Berens ME., Carpten JD., Craig DW., Prados MD.

Data di Pubblicazione: 2017-10-28

Abstract: None

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 29056290

DOI: doi.org/10.1016/j.radonc.2017.09.024

Titolo: The extent of edema and tumor synchronous invasion into the subventricular zone and corpus callosum classify outcomes and radiotherapy strategies of glioblastomas.

Autori: Liang HT., Chen WY., Lai SF., Su MY., You SL., Chen LH., Tseng HM., Chen CM., Kuo SH., Tseng WI.

Data di Pubblicazione: 2017-10-24

Abstract: Our results support the need for developing individualized irradiation strategies for glioblastomas according to EPE and sSVZCC.

Journal Title: Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology

PUBMED ID: 29053887

DOI: doi.org/10.1111/nan.12447

Titolo: Low FoxG1 and high Olig-2 labelling indices define a prognostically favourable subset in isocitrate dehydrogenase (IDH)-mutant gliomas.

Autori: Schäfer S., Behling F., Skardelly M., Koch M., Ott I., Paulsen F., Tabatabai G., Schittenhelm J.

Data di Pubblicazione: 2017-10-21

Abstract: While the combined FoxG1/Olig-2 profile may discriminate H3F3A K27- and G34-mutant tumours and define a prognostically favourable subset in IDH-mutant gliomas, our data show that labelling indices of these transcription factors overlap with adult IDH-mutant and wild-type tumour classes.

Journal Title: Neuropathology and applied neurobiology

PUBMED ID: 29037775

DOI: doi.org/10.1016/j.radonc.2017.09.034

Titolo: Neuroendocrine late effects after tailored photon radiotherapy for children with low grade gliomas: Long term correlation with tumour and treatment parameters.

Autori: Aloï D., Belgioia L., Barra S., Giannelli F., Cavagnetto F., Gallo F., Milanaccio C., Garrè M., Di Profio S., Di Iorgi N., Corvò R.

Data di Pubblicazione: 2017-10-18

Abstract: Radiotherapy showed excellent OS and PFS rates and acceptable late neuroendocrine toxicity profile in this population of LGG patients treated over a period of 13years. In our experience, the dose to the HPA was predictive of the risk of late endocrine toxicity.

Journal Title: Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology

PUBMED ID: 29036345

DOI: doi.org/10.1093/neuonc/nox151

Titolo: Phase II study of cabozantinib in patients with progressive glioblastoma: subset analysis of patients with prior antiangiogenic therapy.

Autori: Cloughesy TF., Drappatz J., de Groot J., Prados MD., Reardon DA., Schiff D., Chamberlain M., Mikkelsen T., Desjardins A., Ping J., Holland J., Weitzman R., Wen PY.

Data di Pubblicazione: 2017-10-17

Abstract: NCT00704288 (<https://www.clinicaltrials.gov/ct2/show/NCT00704288>).

Journal Title: Neuro-oncology

PUBMED ID: 29025274

DOI: doi.org/10.1080/03007995.2017.1392294

Titolo: Overall survival in patients with glioblastoma before and after bevacizumab approval.

Autori: Johnson DR., Omuro AMP., Ravelo A., Sommer N., Guerin A., Ionescu-Itu R., Shi S., Macalalad A., Uhm JH.

Data di Pubblicazione: 2017-10-14

Abstract: The results of this large population-based study suggested an improvement in OS among patients with a GBM diagnosis in 2010-2012 compared to 2006-2008. While the cause of this improvement cannot be proven in a retrospective analysis, the timing of the survival increase coincides with the approval of bevacizumab for the treatment of patients with progressive GBM, indicating a possible benefit of bevacizumab in this population.

Journal Title: Current medical research and opinion

PUBMED ID: 29016998

DOI: doi.org/10.1093/neuonc/nox154

Titolo: Phase II study of cabozantinib in patients with progressive glioblastoma: subset analysis of patients naive to antiangiogenic therapy.

Autori: Wen PY., Drappatz J., de Groot J., Prados MD., Reardon DA., Schiff D., Chamberlain M., Mikkelsen T., Desjardins A., Holland J., Ping J., Weitzman R., Cloughesy TF.

Data di Pubblicazione: 2017-10-11

Abstract: NCT00704288 (<https://www.clinicaltrials.gov/ct2/show/NCT00704288>).

Journal Title: Neuro-oncology

PUBMED ID: 29016943

DOI: doi.org/10.1093/neuonc/nox162

Titolo: Radiologic progression of glioblastoma under therapy-an exploratory analysis of AVAglio.

Autori: Nowosielski M., Ellingson BM., Chinot OL., Garcia J., Revil C., Radbruch A., Nishikawa R., Mason WP., Henriksson R., Saran F., Kickingeder P., Platten M., Sandmann T., Abrey LE., Cloughesy TF., Bendszus M., Wick W.

Data di Pubblicazione: 2017-10-11

Abstract: Progression of glioblastoma under therapy can be characterized radiologically. These radiologic phenotypes are influenced by treatment and develop differently over time with differential outcomes. Complete resolution of contrast enhancement during treatment is a favorable factor for outcome.

Journal Title: Neuro-oncology

PUBMED ID: 29016808

DOI: doi.org/10.1093/neuonc/nox160

Titolo: Molecular differences in IDH wildtype glioblastoma according to MGMT promoter methylation.

Autori: Kessler T., Sahm F., Sadik A., Stichel D., Hertenstein A., Reifenberger G., Zacher A., Sabel M., Tabatabai G., Steinbach J., Sure U., Krex D., Grosu AL., Bewerunge-Hudler M., Jones D., Pfister SM., Weller M., Opitz C., Bendszus M., von Deimling A., Platten M., Wick W.

Data di Pubblicazione: 2017-10-11

Abstract: MGMT promoter methylation status does not define a molecularly distinct glioblastoma subpopulation among untreated tumors. Progressive mMGMT glioblastomas and mMGMT tumors of patients with short survival tend to have more unfavorable molecular profiles.

Journal Title: Neuro-oncology

PUBMED ID: 28990795

DOI: doi.org/10.2217/cns-2017-0001

Titolo: Postprogression survival in patients with glioblastoma treated with concurrent chemoradiotherapy: a routine care cohort study.

Autori: Majewska P., Ioannidis S., Raza MH., Tanna N., Bulbeck H., Williams M.

Data di Pubblicazione: 2017-10-10

Abstract: Glioblastoma is the commonest malignant brain tumor in adults. Most patients develop progressive disease before they die. However, survival after developing progressive disease is infrequently reported. We identified patients with histologically proven disease who were treated with concurrent chemoradiotherapy during 2006-2013. We analyzed overall survival (OS), progression-free survival and postprogression survival (PPS) in relation to age, O6-methylguanine-DNA methyltransferase promoter methylation and extent of surgical resection. We identified 166 patients. Median survival was 13.5 months; 2-year OS was 21.7%. Median progression-free survival and PPS were 7.03 and 4.53 months, respectively. Age and extent of surgical resection were correlated with OS. Only the extent of surgical resection was associated with PPS. Our work suggests that the established prognostic factors for glioblastoma do not appear to help predict PPS.

Journal Title: CNS oncology

PUBMED ID: 28988377

DOI: doi.org/10.1007/s11060-017-2624-4

Titolo: Phase I study of sorafenib and tipifarnib for recurrent glioblastoma: NABTC 05-02.

Autori: Nghiemphu PL., Ebian VA., Wen P., Gilbert M., Abrey LE., Lieberman F., DeAngelis LM., Robins HI., Yung WKA., Chang S., Drappatz J., Mehta MP., Levin VA., Aldape K., Dancey JE., Wright JJ., Prados M., Kuhn J., Cloughesy TF.

Data di Pubblicazione: 2017-10-9

Abstract: Recurrent glioblastoma (GBM) has a very low 6-month progression free survival (PFS) with currently available treatments. Combination chemotherapy to target multiple cell signaling pathways is currently being investigated in order to improve prognosis for recurrent disease. The purpose of this phase I study was to determine the maximum tolerated dose (MTD) for the combination of tipifarnib and sorafenib for the treatment of recurrent GBM. Patients with pathologically proven WHO grade IV GBM and radiographically proven tumor recurrence were eligible for this study. Treatments included sorafenib at twice daily and escalating dosages of tipifarnib. Dose-limiting toxicity

(DLT) was determined over the first 28-days of treatments, and the MTD was determined in a 3+3 study design. We enrolled 24 patients, and 21 patients completed the MTD period. The study was stopped early with no MTD determination for excessive toxicities. The last dose level reached was sorafenib at 200 mg twice a day and tipifarnib 100 mg twice a day on an alternating week schedule. The DLTs included diarrhea, lipase elevation, hypophosphatemia, and arthralgia. The combination of sorafenib and tipifarnib has excessive toxicities and full single agent dosages could not be achieved in combination.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 28986229

DOI: doi.org/10.1016/j.wneu.2017.09.144

Titolo: Analysis of Survival Prognosis for Children with Symptomatic Optic Pathway Gliomas Who Received Surgery.

Autori: Liu Y., Hao X., Liu W., Li C., Gong J., Ma Z., Tian Y.

Data di Pubblicazione: 2017-10-8

Abstract: Surgery is safe and feasible for children with large volumes of OPGs and symptoms of functional impairment and obstructive hydrocephalus. Furthermore, adjuvant RT after surgery may significantly improve OS and PFS. The pathologic grade is an independent prognostic factor for OS, and the age at diagnosis is an independent prognostic factor for PFS.

Journal Title: World neurosurgery

PUBMED ID: 28980418

DOI: doi.org/10.1002/cam4.1171

Titolo: Medulloblastoma in children and adolescents: a systematic review of contemporary phase I and II clinical trials and biology update.

Autori: Bautista F., Fioravanti V., de Rojas T., Carceller F., Madero L., Lassaletta A., Moreno L.

Data di Pubblicazione: 2017-10-6

Abstract: Survival rates for patients with medulloblastoma have improved in the last decades but for those who relapse outcome is dismal and new approaches are needed. Emerging drugs have been tested in the last two decades with in the context of phase I/II trials. In parallel, advances in genetic profiling have permitted to identify key molecular alterations for which new strategies are being developed. We performed a systematic review focused on the design and outcome of early-phase trials evaluating new agents in patients with relapsed medulloblastoma. PubMed, clinicaltrials.gov, and references from selected studies were screened to identify phase I/II studies with reported results between 2000 and 2015 including patients with medulloblastoma aged < 18 years. A total of 718 studies were reviewed and 78 satisfied eligibility criteria. Of those, 69% were phase I; 31% phase II. Half evaluated conventional chemotherapeutics and 35% targeted agents. Overall, 662 patients with medulloblastoma/primitive neuroectodermal tumors were included. The study designs and the response assessments were heterogeneous, limiting the comparisons among trials and the correct identification of active drugs. Median (range) objective response rate (ORR) for patients with medulloblastoma in phase I/II studies was 0% (0-100) and 6.5% (0-50), respectively. Temozolomide containing regimens had a median ORR of 16.5% (0-100). Smoothed inhibitors trials had a median ORR of 8% (3-8). Novel drugs have shown limited activity against relapsed medulloblastoma. Temozolomide might serve as backbone for new combinations. Novel and more homogenous trial designs might facilitate the development of new drugs.

Journal Title: Cancer medicine

PUBMED ID: 28956223

DOI: doi.org/10.1007/s11060-017-2619-1

Titolo: Estimating progression-free survival in patients with glioblastoma using routinely collected data.

Autori: Kelly C., Majewska P., Ioannidis S., Raza MH., Williams M.

Data di Pubblicazione: 2017-9-29

Abstract: Glioblastoma (GBM) represents 80% of all primary malignant brain tumours in adults. Prognosis is poor, and there is a clear correlation between disease progression and deterioration in functional status. In this pilot study we assess whether we can estimate disease progression and progression free survival (PFS) from routinely collected electronic healthcare data. We identified fifty patients with glioblastoma who had chemo-radiotherapy. For each patient we manually collected a reference data set recording demographics, surgery, radiotherapy, chemotherapy, follow-up and death. We also obtained an electronic routine data set for each patient by combining local data on chemotherapy/radiotherapy and hospital admissions. We calculated overall survival (OS) and PFS using the reference data set, and estimated them using the routine data sets using two different methods, and compared the estimated measures with the reference measures. Overall survival was 68% at 1 year and median OS was 12.8 months. The routine data correctly identified progressive disease in 37 of 40 patients and stable disease in 7 of 10 patients. PFS was 7.4 months and the estimated PFS using routine data was 9.1 and 7.8 months with methods 1 and 2 respectively. There was acceptable agreement between reference and routine data in 49 of 50 patients for OS and 35 of 50 patients for PFS. The event of progression, subsequent treatment and OS are well estimated using our approach, but PFS estimation is less accurate. Our approach could refine our understanding of the disease course and allow us to report PFS, OS and treatment nationally.

Journal Title: Journal of neuro-oncology

PUBMED ID: 28946903

DOI: doi.org/10.1186/s13046-017-0600-7

Titolo: High expression of Bruton's tyrosine kinase (BTK) is required for EGFR-induced NF- $\kappa$ B activation and predicts poor prognosis in human glioma.

Autori: Yue C., Niu M., Shan QQ., Zhou T., Tu Y., Xie P., Hua L., Yu R., Liu X.

Data di Pubblicazione: 2017-9-27

Abstract: Taken together, our study suggests that BTK is a novel prognostic marker and molecular therapeutic target for glioma. BTK is required for EGFR-induced NF- $\kappa$ B activation in glioma cells. These findings provide the basis for future clinical studies of ibrutinib for the treatment of glioma.

Journal Title: Journal of experimental & clinical cancer research : CR

PUBMED ID: 28928820

DOI: doi.org/10.3892/ol.2017.6543

Titolo: Management of supratentorial recurrent low-grade glioma: A multidisciplinary experience in 35 adult patients.

Autori: Spitaels J., Devriendt D., Sadeghi N., Luce S., De Witte O., Goldman S., Mélot C., Lefranc F.

Data di Pubblicazione: 2017-9-21

Abstract: The management of recurrent diffuse low-grade gliomas (LGGs) is controversial. In the present study, the multidisciplinary management of 35 patients with recurrent LGGs was retrospectively analyzed. Tumor progression or recurrence was defined by clinical, radiological and/or metabolic pejorative evolution. All patients were regularly followed up by a multidisciplinary neuro-oncological group at Hôpital Erasme. Patients with histologically confirmed supratentorial LGGs (7 astrocytoma, 22 oligodendrogliomas and 6 oligoastrocytomas) who had undergone surgery between August 2004 and November 2010 were included. A total of 3 patients exhibited no tumor progression (median

follow-up (FU), 81 months; range, 68-108 months). Tumor recurrence occurred in the 32 remaining patients [progression-free survival (PFS), 26 months; range, 2-104 months]. In addition, 25/29 (86%) patients who received surgery alone underwent reoperation at the time of tumor recurrence, and high-grade transformation occurred in 6 of these patients (24%). Furthermore, 4/29 (14%) patients were treated with adjuvant therapy alone (3 chemotherapy and 1 radiotherapy). In the 19 patients with no high-grade transformation at reintervention, 3 received adjuvant therapy and 16 were regularly followed up through multimodal imaging. The PFS time of the patients who underwent reoperation with close FU (n=16) and for the patients receiving adjuvant therapy with or without surgery (n=7) at first recurrence was 10 and 24 months (P=0.005), respectively. However, no significant difference was observed for overall survival (P=0.403). At the time of this study, 22 of the 35 patients included were alive following a median FU time of 109 months (range, 55-136). The results of the present study could change the multidisciplinary approach used into a more aggressive approach with adjuvant therapy, with or without surgery, for the treatment of a select subpopulation of patients with LGGs at the first instance of tumor recurrence.

Journal Title: Oncology letters

PUBMED ID: 28927109

DOI: doi.org/10.3892/ol.2017.6630

Titolo: Disease progression patterns of bevacizumab responders with recurrent malignant gliomas.

Autori: Kim JH., Jung TY., Hwang EC., Jung SH., Jung S., Kim IY., Jang WY., Moon KS., Lee KH., Kim SK.

Data di Pubblicazione: 2017-9-21

Abstract: Tumor progression in patients with recurrent malignant glioma who respond to bevacizumab (BEV) is difficult to assess. The current study reviewed the clinical and radiological results of patients following a BEV-based chemotherapy regimen, and evaluated disease progression patterns in patients who responded to BEV therapy. From August 2011 to November 2015, 24 patients (18 glioblastoma cases and 6 anaplastic astrocytoma cases) were treated with BEV-based chemotherapy. In total, 6 patients were treated with BEV alone and 18 patients were treated with BEV combined with irinotecan. The male-female ratio was 10:14, and the median age was 47.5 years (range, 29-69). Patient performance status (PS) was classified using the Eastern Cooperative Oncology Group PS scores as follows: PS 1 (n=3), PS 2 (n=9), PS 3 (n=9) and PS 4 (n=3). Treatment-associated complications were also analyzed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Treatment responses were estimated using the Response Assessment in Neuro-Oncology Criteria. Progression-free survival (PFS) following treatment, patterns of disease progression and overall survival following treatment failure were also analyzed. The median PFS was 2.8 months (range, 0.6-10.1). In total, 2 patients did not continue treatment due to rectal bleeding and severe hematologic toxicity. Amongst the BEV responders (n=16, 72.7%), there was clinical deterioration without significant radiological progression in 2 patients (n=2, 12.5%). Radiological progression of non-enhancing lesions without enhancement flare-ups was observed in 6 patients (42.9%). A total of 3 of those lesions were diffuse and 3 were focal. Increased lesion enhancement was observed in 8 patients (57.1%). Of the non-responders (n=6, 27.3%), diffuse enlargement of non-enhancing lesions was detected in 2 patients and an increase in lesion enhancement occurred in 4 patients. BEV complete responders (n=3) radiologically progressed with enlarged T2/fluid attenuation inversion recovery lesions without enhancement, followed by enhancement flare-ups. Following BEV treatment failure, 8 patients received a number of adjuvant treatments and the overall survival was 4.5 months (range, 0.4-34.0). Clinical symptoms and radiological alterations of non-enhancing lesions must be evalu

ated in order to assess tumor progression in the BEV responders, particularly in patients who have achieved complete remission.  
Journal Title: Oncology letters

PUBMED ID: 28901423

DOI: doi.org/10.3892/mmr.2017.7456

Titolo: A multi-targeted tyrosine kinase inhibitor lenvatinib for the treatment of mice with advanced glioblastoma.

Autori: Li J., Zou CL., Zhang ZM., Lv LJ., Qiao HB., Chen XJ.

Data di Pubblicazione: 2017-9-14

Abstract: Glioblastoma is the most aggressive primary brain tumor that originates from the glial cells in adults. Aberrant angiogenesis is essential for malignant glioblastoma tumorigenesis, development and metastasis. Lenvatinib is a multi-targeted anticancer agent that targets of receptor tyrosine kinases including vascular endothelial growth factor receptor 1 and 2, fibroblast growth factor receptor 1, platelet-derived growth factor receptor  $\beta$  and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog. In the present study, the therapeutic effects of lenvatinib as a treatment for glioblastoma were investigated in vivo and in vitro. The maximum dose toxicity (MDT) and treatment-associated adverse events of lenvatinib were identified by cytotoxicity assay in experimental mice. Increasing levels of the pro-apoptosis genes caspase-3, -8, -9 and -10 following lenvatinib treatment were determined by reverse transcription-quantitative polymerase chain reaction, and apoptosis of the malignant gliomas cells was analyzed by FACS. In vivo treatment with lenvatinib for BV-2 bearing male BALB/c nude mice was assessed via tumor growth suppression and long-term observation of survival. Subsequent cytotoxic T lymphocyte responses were further analyzed to determine the in vivo efficacy of lenvatinib treatment in mice with glioblastoma. The MDT of lenvatinib was identified as 0.24 mg, with relatively few side effects and improved efficacy in mice. Lenvatinib (0.24 mg) significantly increased apoptosis in BV-2, C6, BC3H1 and G422 glioma cell lines. Tumor growth was significantly inhibited and tumor-bearing mice demonstrated an improved survival rate following treatment with lenvatinib. In conclusion, lenvatinib provided an effective treatment outcome, and the results of the present study may help to achieve a comprehensive therapeutic schedule for clinical application.

Journal Title: Molecular medicine reports

PUBMED ID: 28885120

DOI: doi.org/10.3171/2017.3.JNS162383

Titolo: Threshold of the extent of resection for WHO Grade III gliomas: retrospective volumetric analysis of 122 cases using intraoperative MRI.

Autori: Fujii Y., Muragaki Y., Maruyama T., Nitta M., Saito T., Ikuta S., Iseki H., Hongo K., Kawamata T.

Data di Pubblicazione: 2017-9-9

Abstract: OBJECTIVE WHO Grade III gliomas are relatively rare and treated with multiple modalities such as surgery, chemotherapy, and radiotherapy. The impact of the extent of resection (EOR) on improving survival in patients with this tumor type is unclear. Moreover, because of the heterogeneous radiological appearance of Grade III gliomas, the MRI sequence that best correlates with tumor volume is unknown. In the present retrospective study, the authors evaluated the prognostic significance of EOR. METHODS Clinical and radiological data from 122 patients with newly diagnosed WHO Grade III gliomas who had undergone intraoperative MRI-guided resection at a single institution between March 2000 and December 2011 were analyzed retrospectively. Patients were divided into 2 groups by histological subtype: 81 patients had anaplastic astrocytoma (AA) or anaplastic oligoastrocytoma (AOA), and 41 patients had anaplastic oligodendroglioma (AO). EOR was calculated using pre- and postoperative T2-weighted and contrast-enhanced T1-weighted MR images. Univariate

and multivariate analyses were performed to evaluate the prognostic significance of EOR on overall survival (OS). RESULTS The 5-, 8-, and 10-year OS rates for all patients were 74.28%, 70.59%, and 65.88%, respectively. The 5- and 8-year OS rates for patients with AA and AOA were 72.2% and 67.2%, respectively, and the 10-year OS rate was 62.0%. On the other hand, the 5- and 8-year OS rates for patients with AO were 79.0% and 79.0%; the 10-year OS rate is not yet available. The median pre- and postoperative T2-weighted high-signal intensity volumes were 56.1 cm

Journal Title: Journal of neurosurgery

PUBMED ID: 28871999

DOI: doi.org/10.1016/j.ijrobp.2017.04.007

Titolo: Multimodal Magnetic Resonance Imaging of Treatment-Induced Changes to Diffuse Infiltrating Pontine Gliomas in Children and Correlation to Patient Progression-Free Survival.

Autori: Calmon R., Puget S., Varlet P., Beccaria K., Blauwblomme T., Grevent D., Sainte-Rose C., Castel D., Dufour C., Dhermain F., Bolle S., Saitovitch A., Zilbovicius M., Brunelle F., Grill J., Boddaert N.

Data di Pubblicazione: 2017-9-6

Abstract: Multimodal MRI provides useful information about diffuse infiltrating pontine gliomas' response to treatment; rCBV increases following RT, and higher values are correlated with better PFS. High rCBV values following RT should not be mistaken for progression and could be an indicator of response to therapy.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 28868256

DOI: doi.org/10.3389/fonc.2017.00178

Titolo: Multiparametric MRI and [

Autori: Hassanzadeh C., Rao YJ., Chundury A., Rowe J., Ponisio MR., Sharma A., Miller-Thomas M., Tsien CI., Ippolito JE.

Data di Pubblicazione: 2017-9-5

Abstract: Recurrent GBM in the molecular era is associated with highly variable outcomes. Multiparametric MR and FDG-PET biomarkers may provide a clinically relevant, non-invasive and cost-effective method of predicting prognosis and improving clinical decision making in the treatment of patients with suspected tumor recurrence.

Journal Title: Frontiers in oncology

PUBMED ID: 28842741

DOI: doi.org/10.1007/s00234-017-1899-7

Titolo: Response Assessment in Neuro-Oncology criteria, contrast enhancement and perfusion MRI for assessing progression in glioblastoma.

Autori: Tensaouti F., Khalifa J., Lusque A., Plas B., Lotterie JA., Berry I., Laprie A., Cohen-Jonathan Moyal E., Lubrano V.

Data di Pubblicazione: 2017-8-27

Abstract: In conclusion, our findings suggest that CE-3D criterion is not yet suitable to assess progression in routine clinical practice. Indeed, the accurate threshold is still not well defined. To date, in our opinion, early detection of disease progression by RANO combined with advanced MRI imaging techniques like MRI perfusion and diffusion remains the best way to assess disease progression. Further investigations that would examine the impact of treatment modifications after progression determined by different criteria on overall survival would be of great value.

Journal Title: Neuroradiology



PUBMED ID: 28836106

DOI: doi.org/10.1007/s11060-017-2599-1

Titolo: The impact of adjuvant therapy for patients with high-risk diffuse WHO grade II glioma.

Autori: Youland RS., Kreofsky CR., Schomas DA., Brown PD., Buckner JC., Laack NN.

Data di Pubblicazione: 2017-8-25

Abstract: Despite recent randomized, prospective evidence supporting use of RT and chemotherapy (CRT) for high-risk low-grade gliomas (LGG), many patients have historically received RT alone, chemotherapy alone or observation postoperatively. The purpose of this study is to evaluate outcomes for historical treatments in comparison to CRT for high-risk diffuse WHO grade II glioma patients. Records from 309 adults with WHO grade II glioma (1997-2008) eligible for RTOG 9802 (incomplete resection/biopsy or age  $\geq 40$  years) were retrospectively reviewed. Kaplan-Meier estimates were used for progression-free survival (PFS) and overall survival (OS). The Cox proportional hazards model was used for estimates of risk ratios for univariate and multivariate analyses. Median follow-up was 10.6 years. Adjuvant treatments included radiotherapy (RT) alone (45%), observation (31%), CRT (21%) and chemotherapy alone (3%). Non-astrocytic histology, TERT promoter mutation, 1p/19q codeletion and extensive resections were associated with improved PFS and OS on univariate analysis (all  $p < 0.05$ ). IDH mutations and adjuvant CRT was associated with improved PFS (all  $p < 0.05$ ). On multivariate analysis, histology, molecular grouping and extent of resection were significantly associated with PFS and OS. In addition, multivariate analysis revealed that CRT was associated with improved PFS and OS compared with RT alone, and improved PFS compared with observation. This study confirms the benefit of adding chemotherapy to RT compared with RT alone or observation. These findings emphasize the need for aggressive treatment in patients with high-risk LGG.

Journal Title: Journal of neuro-oncology

PUBMED ID: 28824876

DOI: doi.org/10.3389/fonc.2017.00165

Titolo: Gliomatosis Cerebri: Current Understanding and Controversies.

Autori: Ranjan S., Warren KE.

Data di Pubblicazione: 2017-8-22

Abstract: Gliomatosis cerebri (GC) is a rare, extensively infiltrating glioma involving multiple contiguous lobes of the brain. This lethal disease affects all age groups, and the majority of patients have a poor outcome despite aggressive treatment. Despite its initial recognition in 1938, GC remains a controversial entity with little consensus in its definition, histology, or treatment. The majority of GC tumors are astrocytic, although mixed phenotypes have been identified. Treatment of GC is challenging as surgery is generally not an option due to the extensive areas of brain involved, the benefit of radiation therapy is unclear, and no chemotherapy has proven efficacy. Due to the rarity of the disease and its heterogeneity, both at histopathological and molecular levels, it is difficult to conduct clinical trials tailored for this diagnosis. This review summarizes our current knowledge, examines clinical studies focusing on the treatment of GC, highlights ongoing challenges, and discusses the recent molecular insights into adult and pediatric GC. We conclude that, although no longer recognized as a distinct pathological entity, GC represents a unique disease phenotype. Given the histologic and molecular overlap with other diffuse gliomas, the research emphasis should be on investigating its unique invasive biology.

Journal Title: Frontiers in oncology

PUBMED ID: 28791500

DOI: doi.org/10.1007/s00701-017-3277-y

Titolo: Correlation of volumetric growth and histological grade in 50 meningiomas.

Autori: Soon WC., Fountain DM., Koczyk K., Abdulla M., Giri S., Allinson K., Matys T., Guilfoyle MR., Kirollos RW., Santarius T.

Data di Pubblicazione: 2017-8-10

Abstract: Reliable tools now exist to evaluate and monitor volumetric growth of meningiomas. Grade II meningiomas have significantly higher VGR compared with grade I meningiomas and growth of more than 3 cm

Journal Title: Acta neurochirurgica

PUBMED ID: 28748343

DOI: doi.org/10.1007/s11060-017-2575-9

Titolo: A phase I/II study of gemcitabine during radiotherapy in children with newly diagnosed diffuse intrinsic pontine glioma.

Autori: Veldhuijzen van Zanten SEM., El-Khouly FE., Jansen MHA., Bakker DP., Sanchez Aliaga E., Haasbeek CJA., Wolf NI., Zwaan CM., Vandertop WP., van Vurden DG., Kaspers GJL.

Data di Pubblicazione: 2017-7-28

Abstract: The purpose of this phase I/II, open-label, single-arm trial is to investigate the safety, tolerability, maximum tolerated dose and preliminary efficacy of the potential radiosensitizer gemcitabine, administered concomitantly to radiotherapy, in children with newly diagnosed diffuse intrinsic pontine glioma (DIPG). Six doses of weekly gemcitabine were administered intravenously, concomitantly to 6 weeks of hyperfractionated radiotherapy. Successful cohorts received increasing doses of 140, 175 and 200 mg/m

Journal Title: Journal of neuro-oncology

PUBMED ID: 28747219

DOI: doi.org/10.1186/s13256-017-1373-5

Titolo: Role of eculizumab in a pediatric refractory gemcitabine-induced thrombotic microangiopathy: a case report.

Autori: Facchini L., Lucchesi M., Stival A., Roperto RM., Melosi F., Materassi M., Farina S., Tintori V., de Martino M., Sardi I.

Data di Pubblicazione: 2017-7-28

Abstract: Eculizumab prevents serious complement-mediated vascular damage for chemotherapy-induced thrombotic microangiopathy in pediatric cases.

Journal Title: Journal of medical case reports

PUBMED ID: 28727518

DOI: doi.org/10.1200/JCO.2016.71.8726

Titolo: Therapeutic and Prognostic Implications of BRAF V600E in Pediatric Low-Grade Gliomas.

Autori: Lassaletta A., Zapotocky M., Mistry M., Ramaswamy V., Honnorat M., Krishnatry R., Guerreiro Stucklin A., Zhukova N., Arnoldo A., Ryall S., Ling C., McKeown T., Loukides J., Cruz O., de Torres C., Ho CY., Packer RJ., Tatevossian R., Qaddoumi I., Harreld JH., Dalton JD., Mulcahy-Levy J., Foreman N., Karajannis MA., Wang S., Snuderl M., Nageswara Rao A., Giannini C., Kieran M., Ligon KL., Garre ML., Nozza P., Mascelli S., Raso A., Mueller S., Nicolaides T., Silva K., Perbet R., Vasiljevic A., Faure Conter C., Frappaz D., Leary S., Crane C., Chan A., Ng HK., Shi ZF., Mao Y., Finch E., Eisenstat D., Wilson B., Carret AS., Hauser P., Sumerauer D., Krskova L., Larouche V., Fleming A., Zelcer S., Jabado N., Rutka JT., Dirks P., Taylor MD., Chen S., Bartels U., Huang A., Ellison DW., Bouffet E., Hawkins C., Tabori U.

Data di Pubblicazione: 2017-7-21

Abstract: Purpose BRAF V600E is a potentially highly targetable mutation detected in a subset of pediatric low-grade gliomas (PLGGs). Its biologic and c

linical effect within this diverse group of tumors remains unknown. Patients and Methods A combined clinical and genetic institutional study of patients with PLGGs with long-term follow-up was performed (N = 510). Clinical and treatment data of patients with BRAF V600E mutated PLGG (n = 99) were compared with a large international independent cohort of patients with BRAF V600E mutated-PLGG (n = 180). Results BRAF V600E mutation was detected in 69 of 405 patients (17%) with PLGG across a broad spectrum of histologies and sites, including midline locations, which are not often routinely biopsied in clinical practice. Patients with BRAF V600E PLGG exhibited poor outcomes after chemotherapy and radiation therapies that resulted in a 10-year progression-free survival of 27% (95% CI, 12.1% to 41.9%) and 60.2% (95% CI, 53.3% to 67.1%) for BRAF V600E and wild-type PLGG, respectively (P < .001). Additional multivariable clinical and molecular stratification revealed that the extent of resection and CDKN2A deletion contributed independently to poor outcome in BRAF V600E PLGG. A similar independent role for CDKN2A and resection on outcome were observed in the independent cohort. Quantitative imaging analysis revealed progressive disease and a lack of response to conventional chemotherapy in most patients with BRAF V600E PLGG. Conclusion BRAF V600E PLGG constitutes a distinct entity with poor prognosis when treated with current adjuvant therapy.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 28711289

DOI: doi.org/10.1016/j.jocn.2017.06.070

Titolo: Clinical outcomes in recurrent glioblastoma with bevacizumab therapy : An analysis of the literature.

Autori: Tipping M., Eickhoff J., Ian Robins H.

Data di Pubblicazione: 2017-7-17

Abstract: Bevacizumab (BEV) is a common treatment for recurrent glioblastoma (GBM). After progression on BEV, there is no consensus on subsequent therapy, as multiple chemotherapy trials have failed to demonstrate discernible activity for salvage. A previous review (995 patients) estimated a progression free survival (PFS) on BEV of 4.2months (SD±2.1) with an overall survival (OS) after progression on BEV at 3.8months (SD±1). We endeavored to establish a more rigorous historical control, both as a benchmark for efficacy, and a prognostic tool for clinical practice. A comprehensive literature review was performed utilizing PubMed and societal presentation abstracts. A total 2388 patients from 53 arms of 42 studies were analyzed in three groups: 1) thirty-two studies in which survival post-BEV was determined by subtracting PFS from OS (2045 patients): PFS on BEV=4.38months (95% CI 4.09-4.68); OS post-BEV=3.36months (95% CI 3.12-3.66); 2) two studies (94 patients) in which OS post-BEV is reported: OS=3.26 (95% CI 2.39-4.42); 3) eight studies of salvage therapy after progression on BEV (249 patients): of OS post-BEV=4.46months (95% CI 3.68-5.54). These estimates provide a firm historical control for PFS on BEV, as well as OS after disease progression on BEV therapy.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 28708230

DOI: doi.org/10.5301/tj.5000672

Titolo: Short course radiotherapy concomitant with temozolomide in GBM patients: a phase II study.

Autori: Fariselli L., Cuppini L., Gaviani P., Marchetti M., Pinzi V., Milanesi I., Simonetti G., Tramacere I., DiMeco F., Salmaggi A., Silvani A.

Data di Pubblicazione: 2017-7-15

Abstract: To improve local control and OS, a more aggressive treatment schedule should be explored. The related higher necrosis risk and its implications regarding local control deserve further investigation.  
Journal Title: Tumori

PUBMED ID: 28702781

DOI: doi.org/10.1007/s11060-017-2550-5

Titolo: Radiographic patterns of progression with associated outcomes after bevacizumab therapy in glioblastoma patients.

Autori: Cachia D., Elshafeey NA., Kamiya-Matsuoka C., Hatami M., Alfaro-Munoz KD., Mandel JJ., Colen R., DeGroot JF.

Data di Pubblicazione: 2017-7-14

Abstract: Treatment response and survival after bevacizumab failure remains poor in patients with glioblastoma. Several recent publications examining glioblastoma patients treated with bevacizumab have described specific radiographic patterns of disease progression as correlating with outcome. This study aims to scrutinize these previously reported radiographic prognostic models in an independent data set to inspect their reproducibility and potential for clinical utility. Sixty four patients treated at MD Anderson matched predetermined inclusion criteria. Patients were categorized based on previously published data by: (1) Nowosielski et al. into: T2-diffuse, cT1 Flare-up, non-responders and T2 circumscribed groups (2) Modified Pope et al. criteria into: local, diffuse and distant groups and (3) Bahr et al. into groups with or without new diffusion-restricted and/or pre-contrast T1-hyperintense lesions. When classified according to Nowosielski et al. criteria, the cT1 Flare-up group had the longest overall survival (OS) from bevacizumab initiation, with non-responders having the worst outcomes. The T2 diffuse group had the longest progression free survival (PFS) from start of bevacizumab. When classified by modified Pope et al. criteria, most patients did not experience a shift in tumor pattern from the pattern at baseline, while the PFS and OS in patients with local-to-local and local-to-diffuse/distant patterns of progression were similar. Patients developing restricted diffusion on bevacizumab had worse OS. Diffuse patterns of progression in patients treated with bevacizumab are rare and not associated with worse outcomes compared to other radiographic subgroups. Emergence of restricted diffusion during bevacizumab treatment was a radiographic marker of worse OS.

Journal Title: Journal of neuro-oncology

PUBMED ID: 28693286

DOI: doi.org/10.3892/ol.2017.6251

Titolo: Bevacizumab as a last-line treatment for glioblastoma following failure of radiotherapy, temozolomide and lomustine.

Autori: Wenger KJ., Wagner M., You SJ., Franz K., Harter PN., Burger MC., Voss M., Ronellenfitsch MW., Fokas E., Steinbach JP., Bähr O.

Data di Pubblicazione: 2017-7-12

Abstract: In previous trials, bevacizumab failed to prolong the overall survival time in newly diagnosed glioblastoma and at the first recurrence. Randomized clinical trials at the second or further recurrence following the failure of radiotherapy, temozolomide and lomustine, and retrospective analyses focusing on this specific cohort, are not yet available. A total of 62 patients with glioblastoma who received bevacizumab after the failure of standard care, including radiotherapy, temozolomide and lomustine, were retrospectively identified. Patient characteristics, previous treatment details, concomitant therapy, response based on the Response Assessment in Neuro-Oncology criteria, and progression-free survival (PFS) and overall survival (OS) times and rates were evaluated. Furthermore, the PFS and OS times and rates were analyzed for responders and non-responders. Of the patients, 54.8% (n=34) responded to treatment [complete response (CR) 3.2%, n=2; partial response (PR)

51.6%, n=32]. The median PFS time was 3.5 months and the median OS time was 7.5 months. The PFS rate at 6 months was 21.5% and the OS rate at 12 months was 11.5%. Responders (CR or PR) experienced a superior median PFS time compared with non-responders (i.e. stable or progressive disease; 5.4 vs. 1.9 months;  $P<0.0001$ ) and a superior PFS rate at 6 months (34.9 vs. 7.1%;  $P<0.0001$ ). The median OS time (8.6 vs. 6.4 months;  $P<0.0001$ ) and OS rate at 12 months (21.3 vs. 0%;  $P<0.0001$ ) were also superior in patients who exhibited a response to bevacizumab treatment. In conclusion, the objective response rate and the PFS and OS times and rates indicate that bevacizumab has activity in patients with glioblastoma following the failure of radiotherapy, temozolomide, and lomustine. A randomized trial comparing bevacizumab with best supportive care in these patients is advised.

Journal Title: Oncology letters

PUBMED ID: 28686121

DOI: doi.org/10.3171/2017.4.PEDS16668

Titolo: Surgical and molecular considerations in the treatment of pediatric thalamopeduncular tumors.

Autori: Lee RP., Foster KA., Lillard JC., Klimo P., Ellison DW., Orr B., Boop FA.

Data di Pubblicazione: 2017-7-8

Abstract: OBJECTIVE Thalamopeduncular tumors are a group of pediatric low-grade gliomas that arise at the interface of the thalamus and brainstem peduncle. They typically occur within the first 2 decades of life, presenting with progressive spastic hemiparesis. Treatment strategies, including surgical intervention, have varied significantly. The authors present their experience in the treatment of 13 children, ages 2-15 years, with non-neurofibromatosis-related pilocytic astrocytomas located in the thalamopeduncular region. METHODS Between 2003 and 2016, 13 children presenting with progressive spastic hemiparesis due to a pilocytic astrocytoma at the interface of the thalamus and cerebral peduncles were identified. Medical records were reviewed retrospectively for clinical, radiological, pathological, and surgical data. Formalin-fixed, paraffin-embedded tissue was obtained for 12 cases and tested for KIAA1549-BRAF fusion and BRAF V600E point mutation. RESULTS On preoperative diffusion tensor imaging tractography (performed in 12 patients), the ipsilateral corticospinal tract was displaced laterally in 1 case (8.3%), medially in 1 case (8.3%), anterolaterally in 10 cases (83%), and posteriorly in no cases. Ten patients underwent resection via a transtemporal, transchoroidal approach, which was chosen to avoid further damage to motor function in cases of tumors that caused anterolateral or medial corticospinal tract displacement. With this approach, complications included hemianopia, oculomotor palsy, and tremor at a rate of 50%. Among the 12 patients with obtainable follow-up (mean 50.9 months), none received adjuvant therapy, and only 2 (17%) experienced recurrence or progression. KIAA1549-BRAF fusions were present in 10 cases (83%), while BRAF V600E was absent (0%). The 2 fusion-negative tumors had clinical features atypical for the series, including multi-focality and infiltration. CONCLUSIONS Transcortical, transchoroidal resection of thalamopeduncular tumors through the middle temporal gyrus allows for a high rate of gross-total resection and cure. Diffuse tensor tractography is a critical component of the preoperative planning process to determine the location of white matter tracts in proximity. Molecular status may correlate with clinical features, and the presence of BRAF lesions offers an additional target for future novel therapeutics.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 28685405

DOI: doi.org/10.1007/s11060-017-2562-1

Titolo: Impact of removed tumor volume and location on patient outcome in glioblastoma.

Autori: Awad AW., Karsy M., Sanai N., Spetzler R., Zhang Y., Xu Y., Mahan MA

Data di Pubblicazione: 2017-7-8

Abstract: Glioblastoma is an aggressive primary brain tumor with devastatingly poor prognosis. Multiple studies have shown the benefit of wider extent of resection (EOR) on patient overall survival (OS) and worsened survival with larger preoperative tumor volumes. However, the concomitant impact of postoperative tumor volume and eloquent location on OS has yet to be fully evaluated. We performed a retrospective chart review of adult patients treated for glioblastoma from January 2006 through December 2011. Adherence to standardized postoperative chemoradiation protocols was used as an inclusion criterion. Detailed volumetric and location analysis was performed on immediate preoperative and immediate postoperative magnetic resonance imaging. Cox proportional hazard modeling approach was employed to explore the modifying effects of EOR and eloquent location after adjusting for various confounders and associated characteristics, such as preoperative tumor volume and demographics. Of the 471 screened patients, 141 were excluded because they did not meet all inclusion criteria. The mean ( $\pm$ SD) age of the remaining 330 patients (60.6% male) was  $58.9 \pm 12.9$  years; the mean preoperative and postoperative Karnofsky performance scores (KPSs) were  $76.2 \pm 10.3$  and  $80.0 \pm 16.6$ , respectively. Preoperative tumor volume averaged  $33.2 \pm 29.0$  ml, postoperative residual was  $4.0 \pm 8.1$  ml, and average EOR was  $88.6 \pm 17.6\%$ . The observed average follow-up was  $17.6 \pm 15.7$  months, and mean OS was  $16.7 \pm 14.4$  months. Survival analysis showed significantly shorter survival for patients with lesions in periventricular ( $16.8 \pm 1.7$  vs.  $21.5 \pm 1.4$  mo,  $p=0.03$ ), deep nuclei/basal ganglia ( $11.6 \pm 1.7$  vs.  $20.6 \pm 1.2$ ,  $p=0.002$ ), and multifocal ( $12.0 \pm 1.4$  vs.  $21.3 \pm 1.3$  months,  $p=0.0001$ ) locations, but no significant influence on survival was seen for eloquent cortex sites ( $p=0.14$ , range 0.07-0.9 for all individual locations). OS significantly improved with EOR in univariate analysis, averaging 22.3, 19.7, and 13.2 months for  $>90$ , 80-90, and 70-80% resection, respectively. Survival was 22.8, 19.0, and 12.7 months for 0, 0-5, and 5-10 ml postoperative residual, respectively. A hazard model showed that larger preoperative tumor volume [hazard ratio (HR) 1.05, 95% CI 1.02-1.07], greater age (HR 1.02, 95% CI 1.01-1.03), multifocality (HR 1.44, 95% CI 1.01-2.04), and deep nuclei/basal ganglia (HR 2.05, CI 1.27-3.3) were the most predictive of poor survival after adjusting for KPS and tumor location. There was a negligible but significant interaction between EOR and preoperative tumor volume (HR 0.9995, 95% CI 0.9993-0.9998), but EOR alone did not correlate with OS after adjusting for other factors. The interaction between EOR and preoperative tumor volume represented tumor volume removed during surgery. In conclusion, EOR alone was not an important predictor of outcome during GBM treatment once preoperative tumor volume, age, and deep nuclei/basal ganglia location were factored. Instead, the interaction between EOR and preoperative volume, representing reduced disease burden, was an important predictor of reducing OS. Removal of tumor from eloquent cortex did not impact postoperative KPS. These results suggest aggressive surgical treatment to reduce postoperative residual while maintaining postoperative KPS may aid patient survival outcomes for a given tumor size and location.

Journal Title: Journal of neuro-oncology

PUBMED ID: 28685404

DOI: doi.org/10.1007/s11060-017-2537-2

Titolo: Analysis of factors influencing the access to concomitant chemo-radiotherapy in elderly patients with high grade gliomas: role of MMSE, age and tumor volume.

Autori: Di Cristofori A., Zarino B., Fanizzi C., Fornara GA., Bertani G., Rampini P., Carrabba G., Caroli M.

Data di Pubblicazione: 2017-7-8

Abstract: High grade gliomas (HGG) are tumors with a rapidly progressive course and the standard of care consists of surgery and chemo-radiotherapy. Elderly patients with HGG usually have a worse prognosis due to their comorbidities and difficulties in accessing or completing adjuvant treatments. The purpose of our study was to assess the influence of pre-operative factors (MMSE, age, sex, KPS, tumor volume) on the post-operative access to chemo-radiotherapy in the elderly population. In addition, the influence of the access to adjuvant therapies on overall survival (OS) was assessed. We retrospectively reviewed our consecutive case series of 117 elderly patients ( $\geq 65$  years) with HGG treated in our Institution. All the clinical records regarding age, sex, tumor location, MMSE, KPS, access to adjuvant treatments and OS were analyzed. 72 males and 45 females with a median age of 71 years were analyzed. Adjuvant therapies were considered; concomitant chemo-radiotherapy with standard radiotherapy or hypofractionated radiation regimen. 84 patients had access to adjuvant therapies. Access to therapies was associated with a median age of 71(range 66-80) years, a median MMSE of 26(range 5-30), and a median tumor volume of 24 cm

Journal Title: Journal of neuro-oncology

PUBMED ID: 28683323

DOI: doi.org/10.1016/j.celrep.2017.06.036

Titolo: Identification of a Druggable Pathway Controlling Glioblastoma Invasiveness.

Autori: Pencheva N., de Gooijer MC., Vis DJ., Wessels LFA., Würdinger T., van Tellingen O., Bernards R.

Data di Pubblicazione: 2017-7-7

Abstract: Diffuse and uncontrollable brain invasion is a hallmark of glioblastoma (GBM), but its mechanism is understood poorly. We developed a 3D ex vivo organotypic model to study GBM invasion. We demonstrate that invading GBM cells upregulate a network of extracellular matrix (ECM) components, including multiple collagens, whose expression correlates strongly with grade and clinical outcome. We identify interferon regulatory factor 3 (IRF3) as a transcriptional repressor of ECM factors and show that IRF3 acts as a suppressor of GBM invasion. Therapeutic activation of IRF3 by inhibiting casein kinase 2 (CK2)-a negative regulator of IRF3-downregulated the expression of ECM factors and suppressed GBM invasion in ex vivo and in vivo models across a panel of patient-derived GBM cell lines representative of the main molecular GBM subtypes. Our data provide mechanistic insight into the invasive capacity of GBM tumors and identify a potential therapy to inhibit GBM invasion.

Journal Title: Cell reports

PUBMED ID: 28678383

DOI: doi.org/10.1002/cncr.30838

Titolo: The role of early magnetic resonance imaging in predicting survival on bevacizumab for recurrent glioblastoma: Results from a prospective clinical trial (CABARET).

Autori: Field KM., Phal PM., Fitt G., Goh C., Nowak AK., Rosenthal MA., Sime S J., Barnes EH., Sawkins K., Cher LM., Hovey EJ., Wheeler H.

Data di Pubblicazione: 2017-7-6

Abstract: In this study, early progression on MRI appears to be a robust marker of a poor prognosis for patients on bevacizumab. Cancer 2017;123:3576-82 . © 2017 American Cancer Society.

Journal Title: Cancer

PUBMED ID: 28675067

DOI: doi.org/10.1080/0284186X.2017.1332780

Titolo: Postoperative neoadjuvant temozolomide before radiotherapy versus standard radiotherapy in patients 60 years or younger with anaplastic astrocytoma or glioblastoma: a randomized trial.

Autori: Malmström A., Poulsen HS., Grønberg BH., Stragliotto G., Hansen S., Asklund T., Holmlund B., Łysiak M., Dowsett J., Kristensen BW., Söderkvist P., Rosell J., Henriksson R., Henriksson R.

Data di Pubblicazione: 2017-7-5

Abstract: No advantage of NeoTMZ was noted for the overall study population or subgroup of GBM, while NeoTMZ resulted in 5 years longer median survival for patients diagnosed as AA.

Journal Title: Acta oncologica (Stockholm, Sweden)

PUBMED ID: 28666368

DOI: doi.org/10.1093/neuonc/nox121

Titolo: Cost-effectiveness of radiation and chemotherapy for high-risk low-grade glioma.

Autori: Qian Y., Maruyama S., Kim H., Pollom EL., Kumar KA., Chin AL., Harris JP., Chang DT., Pitt A., Bendavid E., Owens DK., Durkee BY., Soltys SG.

Data di Pubblicazione: 2017-7-2

Abstract: The addition of PCV to RT is a cost-effective treatment strategy for patients with high-risk LGG.

Journal Title: Neuro-oncology

PUBMED ID: 28649001

DOI: doi.org/10.1016/j.ejca.2017.04.019

Titolo: A European randomised controlled trial of the addition of etoposide to standard vincristine and carboplatin induction as part of an 18-month treatment programme for childhood ( $\leq 16$  years) low grade glioma - A final report.

Autori: Gnekow AK., Walker DA., Kandels D., Picton S., Giorgio Perilongo, Grill J., Stokland T., Sandstrom PE., Warmuth-Metz M., Pietsch T., Giangaspero F., Schmidt R., Faldum A., Kilmartin D., De Paoli A., De Salvo GL., De Salvo GL.

Data di Pubblicazione: 2017-6-27

Abstract: The addition of etoposide to VC did not improve PFS or OS. High non-progression rates at 24 weeks justify retaining VC as standard first-line therapy. Infants with diencephalic syndrome and early progression need new treatments to be tested. Future trials should use neurological/visual and toxicity outcomes and be designed to discriminate between the impact on disease outcomes of 'duration of therapy' and 'age at stopping therapy'.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 28647829

DOI: doi.org/10.1007/s10072-017-3036-0

Titolo: Extra central nervous system metastases from glioblastoma: a new possible trigger event?

Autori: Simonetti G., Silvani A., Fariselli L., Hottinger AF., Pesce GA., Prada F., Gaviani P.

Data di Pubblicazione: 2017-6-26

Abstract: Extra-cranial metastases of glioblastoma (GBM) represent a rare event, and the biological-genetic mechanisms involved in the pathogenesis have not yet been determined. We report the case of a young patient with multiple visceral and osseous metastases occurred after 4 years after first diagnosis of GBM. The strangeness as well as the rarity of this event does not allow t



o identify an effective treatment for GBM metastases, making the management of this ominous tumor an even greater challenge.

Journal Title: Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology

PUBMED ID: 28640702

DOI: doi.org/10.1200/JCO.2017.72.6737

Titolo: Diffuse Infiltrating Oligodendroglioma and Astrocytoma.

Autori: van den Bent MJ., Smits M., Kros JM., Chang SM.

Data di Pubblicazione: 2017-6-23

Abstract: The new 2016 WHO brain tumor classification defines different diffuse gliomas primarily according to the presence or absence of IDH mutations (IDH-mt) and combined 1p/19q loss. Today, the diagnosis of anaplastic oligodendroglioma requires the presence of both IDH-mt and 1p/19q co-deletion, whereas anaplastic astrocytoma is divided into IDH wild-type (IDH-wt) and IDH-mt tumors. IDH-mt tumors have a more favorable prognosis, and tumors with low-grade histology especially tend to evolve slowly. IDH-wt tumors are not a homogeneous entity and warrant further molecular testing because some have glioblastoma-like molecular features with poor clinical outcome. Treatment consists of a resection that should be as extensive as safely possible, radiotherapy, and chemotherapy. Trials of patients with newly diagnosed grade II or III glioma have shown survival benefit from adding chemotherapy to radiotherapy compared with initial treatment using radiotherapy alone. Both temozolomide and the combination of procarbazine, lomustine, and vincristine provide survival benefit. In contrast, trials that compare single modality treatment of chemotherapy alone with radiotherapy alone did not observe survival differences. Currently, for patients with grade II or III gliomas who require postsurgical treatment, the preferred treatment consists of a combination of radiotherapy and chemotherapy. Low-grade gliomas with favorable characteristics are slow-growing tumors. When deciding on the timing of postsurgical treatment with radiotherapy and chemotherapy, both clinical and molecular factors should be taken into account, but a more conservative approach can be considered initially in some of these patients. The factor that best predicts benefit of chemotherapy in grade II and III glioma remains to be established.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 28623604

DOI: doi.org/10.1007/s11060-017-2525-6

Titolo: Craniospinal irradiation for treatment of metastatic pediatric low-grade glioma.

Autori: Tsang DS., Murphy ES., Ezell SE., Lucas JT., Tinkle C., Merchant TE.

Data di Pubblicazione: 2017-6-18

Abstract: Patients with disseminated pediatric low-grade glioma (LGG) initially treated with chemotherapy frequently experience disease progression, with 5-year event-free survival (EFS) of <20% and 10-year overall survival (OS) of approximately 70%. This study aimed to describe outcomes of metastatic pediatric LGG treated with craniospinal irradiation (CSI). A retrospective study was performed of all patients with metastatic pediatric LGG treated with CSI at a single institution. EFS was defined as survival without disease progression or secondary high-grade glioma. Dates were counted from the first day of irradiation. We identified 12 eligible patients; all had histologically confirmed LGG. Metastatic disease was present at initial presentation in 9 patients. The median age at CSI was 9.3 years. The 5-year EFS and OS were 71% (95% CI 33.7-89.5) and 70% (95% CI 32.9-89.2), respectively. No deaths were observed among the patients who underwent subtotal resection (STR) before radiotherapy, whereas 3 patients who had undergone biopsy died (OS log-rank

P=0.01). EFS may be longer among patients who underwent STR before RT (EFS log-rank P=0.03), with a hazard ratio for biopsy of 8.4 (vs. STR; 95% CI 0.8-84.0, P=0.07). No patient experienced acute toxicity of grade 3 or higher. Patients with metastatic pediatric LGG treated with CSI experienced longer EFS than historical cohorts treated with chemotherapy alone, with similar OS. CSI may be considered in the management of metastatic pediatric LGG, particularly in older children experiencing progression after chemotherapy.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 28620243  
DOI: doi.org/10.1038/s41598-017-03785-8  
Titolo: Targeting glioma stem cells in vivo by a G-quadruplex-stabilizing synthetic macrocyclic hexaoxazole.  
Autori: Nakamura T., Okabe S., Yoshida H., Iida K., Ma Y., Sasaki S., Yamori T., Shin-Ya K., Nakano I., Nagasawa K., Seimiya H.  
Data di Pubblicazione: 2017-6-17  
Abstract: G-quadruplex (G4) is a higher-order nucleic acid structure that is formed by guanine-rich sequences. G4 stabilization by small-molecule compounds called G4 ligands often causes cytotoxicity, although the potential medicinal impact of this effect has not been fully established. Here we demonstrate that a synthetic G4 ligand, Y2H2-6M(4)-oxazole telomestatin derivative (6OTD), limits the growth of intractable glioblastoma (grade IV glioma) and glioma stem cells (GSCs). Experiments involving a human cancer cell line panel and mouse xenografts revealed that 6OTD exhibits antitumor activity against glioblastoma. 6OTD inhibited the growth of GSCs more potently than it did the growth of differentiated non-stem glioma cells (NSGCs). 6OTD caused DNA damage, G1 cell cycle arrest, and apoptosis in GSCs but not in NSGCs. These DNA damage foci tended to colocalize with telomeres, which contain repetitive G4-forming sequences. Compared with temozolomide, a clinical DNA-alkylating agent against glioma, 6OTD required lower concentrations to exert anticancer effects and preferentially affected GSCs and telomeres. 6OTD suppressed the intracranial growth of GSC-derived tumors in a mouse xenograft model. These observations indicate that 6OTD targets GSCs through G4 stabilization and promotion of DNA damage responses. Therefore, G4s are promising therapeutic targets for glioblastoma.  
Journal Title: Scientific reports

PUBMED ID: 28602885  
DOI: doi.org/10.1016/j.wneu.2017.05.165  
Titolo: High Expression of Glypican-1 Predicts Dissemination and Poor Prognosis in Glioblastomas.  
Autori: Saito T., Sugiyama K., Hama S., Yamasaki F., Takayasu T., Nosaka R., Onishi S., Muragaki Y., Kawamata T., Kurisu K.  
Data di Pubblicazione: 2017-6-13  
Abstract: GPC-1 expression significantly correlated with OS in patients with GBM who received radiotherapy and temozolomide treatment. GPC-1 expression can help predict the occurrence of dissemination and shorter OS in patients with GBM.  
Journal Title: World neurosurgery

PUBMED ID: 28592748  
DOI: doi.org/10.2176/nmc.ra.2017-0018  
Titolo: Epigenetic Targeted Therapy for Diffuse Intrinsic Pontine Glioma.  
Autori: Hashizume R.  
Data di Pubblicazione: 2017-6-9

**Abstract:** Diffuse intrinsic pontine glioma (DIPG) is a rare but uniformly fatal cancer of the brain, with peak incidence in children of 5-7 years of age. In contrast to most types of human cancer, there has been no significant improvement in treatment outcomes for patients with DIPG. Since DIPG occurs in the brainstem, a vital region of the brain, there are no surgical options for providing relief to patients, and chemotherapy as well as radiation therapy provide palliative relief at best. To date, more than 250 clinical trials evaluating radiotherapy along with conventional cytotoxic chemotherapy, as well as newer biologic agents, have failed to improve the dismal outcome when compared with palliative radiation alone. The recent discovery of somatic oncogenic histone gene mutations affecting chromatin regulation in DIPG has dramatically improved our understanding of the disease pathogenesis in DIPG, and these findings have stimulated the development of novel therapeutic approaches targeting epigenetic regulators for disease treatment. This review will discuss about the role of histone modification in chromatin machinery and epigenetic therapeutic strategies for the treatment of DIPG.

**Journal Title:** Neurologia medico-chirurgica

PUBMED ID: 28574607

DOI: doi.org/10.1111/nan.12415

**Titolo:** Prognostic value of O-6-methylguanine-DNA methyltransferase (MGMT) protein expression in glioblastoma excluding nontumour cells from the analysis.

**Autori:** Dahlrot RH., Dowsett J., Fosmark S., Malmström A., Henriksson R., Boldt H., de Stricker K., Sørensen MD., Poulsen HS., Lysiak M., Söderkvist P., Rosell J., Hansen S., Kristensen BW.

**Data di Pubblicazione:** 2017-6-3

**Abstract:** Our data indicate that MGMT protein expression in tumour cells has an independent prognostic significance. Exclusion of nontumour cells contributed to a more exact analysis of tumour-specific MGMT protein expression. This should be incorporated in future studies evaluating MGMT status before potential integration into clinical practice.

**Journal Title:** Neuropathology and applied neurobiology

PUBMED ID: 28556364

DOI: doi.org/10.1111/cas.13285

**Titolo:** Phase I study of glasdegib (PF-04449913), an oral smoothened inhibitor, in Japanese patients with select hematologic malignancies.

**Autori:** Minami Y., Minami H., Miyamoto T., Yoshimoto G., Kobayashi Y., Munakata W., Onishi Y., Kobayashi M., Ikuta M., Chan G., Woolfson A., Ono C., Shaik MN., Fujii Y., Zheng X., Naoe T.

**Data di Pubblicazione:** 2017-5-31

**Abstract:** The hedgehog signaling pathway regulates multiple morphogenetic processes during embryogenesis. Aberrant activation of the hedgehog pathway signal transduction in adult tissues is associated with the pathogenesis of hematologic malignancies and solid tumors. We report findings from an open-label, multicenter phase I trial of the selective, small-molecule hedgehog signaling inhibitor glasdegib (PF-04449913) in Japanese patients with select advanced hematologic malignancies. Glasdegib was administered as once-daily oral doses (25, 50 and 100 mg) in 28-day cycles after a lead-in dose on Day -5. The primary objectives were to determine first-cycle dose-limiting toxicities, safety, vital signs and laboratory test abnormalities. Secondary objectives included evaluation of pharmacokinetics, pharmacodynamics and preliminary evidence of clinical activity of glasdegib. No dose-limiting toxicities were noted in the 13 patients in the present study. All patients experienced at least one treatment-emergent, all-causality adverse event. The most frequent treatment-related adverse events (observed in  $\geq 3$  patients) were dysgeusia (n = 9), muscle spasms (n = 5), alopecia, decreased appetite (n = 4 each), an

d increased blood creatinine phosphokinase, constipation and diarrhea (n = 3 each). Two deaths occurred during the study and were deemed not to be treatment-related due to disease progression. Glasdegib demonstrated dose-proportional pharmacokinetics, marked downregulation of the glioma-associated transcriptional regulator GLI1 expression in normal skin, and evidence of preliminary clinical activity, although data are limited. Glasdegib was safe and well tolerated across the dose levels tested. It is confirmed that the 100-mg dose is safe and tolerable in Japanese patients, and this dose level will be examined in the future clinical trial.  
Journal Title: Cancer science

PUBMED ID: 28544128  
DOI: doi.org/10.1002/pbc.26621  
Titolo: A pediatric trial of radiation/cetuximab followed by irinotecan/cetuximab in newly diagnosed diffuse pontine gliomas and high-grade astrocytomas: A Pediatric Oncology Experimental Therapeutics Investigators' Consortium study.  
Autori: Macy ME., Kieran MW., Chi SN., Cohen KJ., MacDonald TJ., Smith AA., Etzl MM., Kuei MC., Donson AM., Gore L., DiRenzo J., Trippett TM., Ostrovna I., Narendran A., Foreman NK., Dunkel IJ.  
Data di Pubblicazione: 2017-5-26  
Abstract: The trial did not meet the predetermined endpoint to deem this regimen successful for HGA. While the trial met the predetermined endpoint for DIPG, overall survival was not markedly improved from historical controls, therefore does not merit further study in this population.  
Journal Title: Pediatric blood & cancer

PUBMED ID: 28513547  
DOI: doi.org/10.3390/genes8050145  
Titolo: Epigenetic Regulation of Telomere Maintenance for Therapeutic Interventions in Gliomas.  
Autori: Naderlinger E., Holzmann K.  
Data di Pubblicazione: 2017-5-18  
Abstract: High-grade astrocytoma of WHO grade 4 termed glioblastoma multiforme (GBM) is a common human brain tumor with poor patient outcome. Astrocytoma demonstrates two known telomere maintenance mechanisms (TMMs) based on telomerase activity (TA) and on alternative lengthening of telomeres (ALT). ALT is associated with lower tumor grades and better outcome. In contrast to ALT, regulation of TA in tumors by direct mutation and epigenetic activation of the hTERT promoter is well established. Here, we summarize the genetic background of TMMs in non-malignant cells and in cancer, in addition to clinical and pathological features of gliomas. Furthermore, we present new evidence for epigenetic mechanisms (EMs) involved in regulation of ALT and TA with special emphasis on human diffuse gliomas as potential therapeutic drug targets. We discuss the role of TMM associated telomeric chromatin factors such as DNA and histone modifying enzymes and non-coding RNAs including microRNAs and long telomeric TERRA transcripts.  
Journal Title: Genes

PUBMED ID: 28511812  
DOI: doi.org/10.1016/j.pediatrneurol.2017.04.008  
Titolo: Acute Management of Symptomatic Subependymal Giant Cell Astrocytoma With Everolimus.  
Autori: Arroyo MS., Krueger DA., Broomall E., Stevenson CB., Franz DN.  
Data di Pubblicazione: 2017-5-18

Abstract: Everolimus can effectively reduce tumor size, decrease cerebrospinal fluid protein, and allow successful ventriculoperitoneal shunt placement without the need for surgical resection of a symptomatic SEGA.

Journal Title: Pediatric neurology

PUBMED ID: 28500559

DOI: doi.org/10.1007/s11060-017-2466-0

Titolo: Nivolumab for patients with recurrent glioblastoma progressing on bevacizumab: a retrospective case series.

Autori: Chamberlain MC., Kim BT.

Data di Pubblicazione: 2017-5-14

Abstract: A single institution retrospective evaluation of nivolumab following disease progression on bevacizumab in adults with recurrent glioblastoma (GBM) with an objective of determining progression free survival (PFS). There is no accepted therapy for recurrent GBM after failure of bevacizumab. 16 adults, ages 52-72 years (median 62), with recurrent GBM were treated. All patients had previously been treated with surgery, concurrent radiotherapy and temozolomide, and post-radiotherapy temozolomide. Bevacizumab (with or without lomustine) was administered to all patients at first recurrence. Patients were treated with nivolumab only (3 mg/kg) once every 2 weeks at second recurrence. One cycle of nivolumab was defined as 2 treatments. Neurological evaluation was performed bi-weekly and neuroradiographic assessment every 4 weeks. A total of 37 treatment cycles (median 2) were administered of nivolumab in which there were 14 Grade 2 adverse events (AEs) and Grade 3 AEs in two patients. No Grade 4 or 5 AEs were seen. Following 1 month of nivolumab, seven patients demonstrated progressive disease and discontinued therapy. No patient demonstrated a response though nine patients demonstrated neuroradiographic stable response. Survival in the entire cohort ranged from 2 to 6 months with a median of 3.5 months (CI 2.8, 4.2). Median and 6-month PFS at 6 months was 2.0 months (range 1-5 months; CI 1.3, 2.7) and 0% respectively. Nivolumab salvage therapy demonstrated no survival advantage in patients with recurrent bevacizumab refractory GBM emphasizing a continued unmet need in neuro-oncology.

Journal Title: Journal of neuro-oncology

PUBMED ID: 28496000

DOI: doi.org/10.18632/oncotarget.17322

Titolo: Stratification according to recursive partitioning analysis predicts outcome in newly diagnosed glioblastomas.

Autori: Yang F., Yang P., Zhang C., Wang Y., Zhang W., Hu H., Wang Z., Qiu X., Jiang T.

Data di Pubblicazione: 2017-5-13

Abstract: Glioblastoma accounts for more than half of diffuse gliomas. The prognosis of patients with glioblastoma remains poor despite comprehensive and intensive treatments. Furthermore, the clinical significance of molecular parameters and routinely available clinical variables for the prognosis prediction of glioblastomas remains limited. The authors describe a novel model may help in prognosis prediction and clinical management of glioblastoma patients. We performed a recursive partitioning analysis to generate three independent prognostic classes of 103 glioblastomas patients from TCGA dataset. Class I (MGMT promoter methylated, age <58), class II (MGMT promoter methylation, age ≥58; MGMT promoter unmethylation, age <54, KPS ≥70; MGMT promoter unmethylation, age ≥59, KPS ≥70), class III (MGMT promoter unmethylation, age 54-58, KPS ≥70; MGMT promoter unmethylation, KPS <70). Age, KPS and MGMT promoter methylation were the most significant prognostic factors for overall survival. The results were validated in CGGA dataset. This was the first study to combine various molecular parameters and clinical factors into recursive partitioning analysis to predict the prognosis of patients with glioblastoma.

mas. We included MGMT promoter methylation in our study, which could give better suggestion to patients for their chemotherapy. This clinical study will serve as the backbone for the future incorporation of molecular prognostic markers currently in development. Thus, our recursive partitioning analysis model for glioblastomas may aid in clinical prognosis evaluation.  
Journal Title: Oncotarget

PUBMED ID: 28485350  
DOI: doi.org/10.4103/0019-509X.204774  
Titolo: A case series of salvage CCNU in high-grade glioma who have previously received temozolomide from a tertiary care institute in Mumbai.  
Autori: Patil VM., Abhinav R., Tonse R., Epari S., Gupta T., Jalali R.  
Data di Pubblicazione: 2017-5-10  
Abstract: CCNU is associated with modest treatment outcomes in recurrent/relapsed high-grade gliomas. The high rate of myelosuppression is a concern. Urgent efforts are required to improve upon these results.  
Journal Title: Indian journal of cancer

PUBMED ID: 28480352  
DOI: doi.org/10.21010/ajtcam.v13i6.1  
Titolo: TREATMENT OF PROGRESSION OF DIFFUSE ASTROCYTOMA BY HERBAL MEDICINE: CASE REPORT.  
Autori: Trogrlić I., Trogrlić D., Trogrlić Z.  
Data di Pubblicazione: 2017-5-9  
Abstract: The results presented in this research paper clearly indicate the potential of phytotherapy in the treatment of some types of brain tumours. A complete regression of tumour following the treatment with nothing but herbal medicine offers support for such claim. Future research should demonstrate the effectiveness of phytotherapy, as a supplementary form of brain tumour treatment, and the results of this research should be compared with the existing information on the effectiveness of the protocols currently used in the treatment of these types of tumour.  
Journal Title: African journal of traditional, complementary, and alternative medicines : AJTCAM

PUBMED ID: 28470383  
DOI: doi.org/10.1007/s00381-017-3431-0  
Titolo: Tumor treating fields in pediatric high-grade glioma.  
Autori: Green AL., Mulcahy Levy JM., Vibhakkar R., Hemenway M., Madden J., Foreman N., Dorris K.  
Data di Pubblicazione: 2017-5-5  
Abstract: The tolerability of TTF, combined with the adult data, justify a pediatric clinical trial.  
Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 28429093  
DOI: doi.org/10.1007/s10014-017-0285-9  
Titolo: A case of glioblastoma resected immediately after administering bevacizumab: consideration on histopathological findings and safety of surgery.  
Autori: Tokuda Y., Tamura R., Ohara K., Yoshida K., Sasaki H.  
Data di Pubblicazione: 2017-4-22  
Abstract: Surgery after administering bevacizumab should be carefully considered particularly because of wound healing concerns. A 27-year-old man presented with multiple tumor recurrences after gross total removal of a left temporal oligodendroglioma (1p/19q-noncodeleted). Whole brain radiotherapy with

concomitant temozolomide and bevacizumab was immediately prescribed; however, the patient's condition deteriorated because of brain herniation. Three days after administering bevacizumab, an emergency tumor removal with external decompression and a ventriculo-peritoneal shunt was performed. The surgery and postoperative clinical course were uneventful. On histopathological examination, the tumor showed findings such as tumor vessel thrombosis, numerous interstitial red blood cells, and cells with degraded, fragmented nuclei possibly suggesting apoptosis, which could be attributable to bevacizumab. Performing craniotomy shortly after administering bevacizumab is not recommended; however, it can still be safely performed as long as surgery and wound management is carefully performed. Vessel thrombosis might be among the mechanisms of action of bevacizumab.

Journal Title: Brain tumor pathology

PUBMED ID: 28407030

DOI: doi.org/10.1093/annonc/mdx169

Titolo: Intratumoral heterogeneity: pathways to treatment resistance and relapse in human glioblastoma.

Autori: Qazi MA., Vora P., Venugopal C., Sidhu SS., Moffat J., Swanton C., Singh SK.

Data di Pubblicazione: 2017-4-14

Abstract: Intratumoral heterogeneity (ITH) has increasingly being described for multiple cancers as the root cause of therapy resistance. Recent studies have started to explore the scope of ITH in glioblastoma (GBM), a highly aggressive and fatal form of brain tumor, to explain its inevitable therapy resistance and disease relapse. In this review, we detail the emerging data that explores the extensive genetic, cellular and functional ITH present in GBM. We discuss current experimental models of human GBM recurrence and suggest harnessing new technologies (CRISPR-Cas9 screening, CyTOF, cellular barcoding, single cell analysis) to delineate GBM ITH and identify treatment-refractory cell populations, thus opening new therapeutic windows. We will also explore why current therapeutics have failed in clinical trials and how ITH can inform us on developing empiric therapies for the treatment of recurrent GBM.

Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 28382223

DOI: doi.org/10.4103/jpi.jpi\_43\_16

Titolo: Identification of Histological Correlates of Overall Survival in Lower Grade Gliomas Using a Bag-of-words Paradigm: A Preliminary Analysis Based on Hematoxylin & Eosin Stained Slides from the Lower Grade Glioma Cohort of The Cancer Genome Atlas.

Autori: Powell RT., Olar A., Narang S., Rao G., Sulman E., Fuller GN., Rao A.

Data di Pubblicazione: 2017-4-7

Abstract: Here, we demonstrated one potential strategy to incorporate image features derived from H and E stained slides into predictive models of OS. In addition, we showed how these image-derived phenotypic characteristics correlate with molecular signaling activity underlying the etiology or behavior of LGG.

Journal Title: Journal of pathology informatics

PUBMED ID: 28380636

DOI: doi.org/10.1093/neuonc/nox002

Titolo: The role of image-guided intensity modulated proton therapy in glioma.

Autori: Grosshans DR., Mohan R., Gondi V., Shih HA., Mahajan A., Brown PD.

Data di Pubblicazione: 2017-4-6

Abstract: Gliomas represent a broad spectrum of disease with life-expectancy outcomes ranging from months to decades. As our understanding of the molecular profiles of gliomas expands rapidly, practitioners are now better able to identify patients with favorable versus nonfavorable prognoses. Radiation therapy plays a key role in glioma treatment, improving disease control and oftentimes survival. However, for survivors, either long-term or short-term, radiation-induced cognitive impairments may negatively impact their quality of life. For patients with both favorable and unfavorable prognoses, intensity modulated proton therapy (IMPT) may offer significant, yet unproven benefits. IMPT is the newest and most advanced proton delivery technique, one with substantial benefits compared with historical proton techniques. IMPT allows practitioners to maximize the physical benefits of protons, increasing normal tissue sparing and reducing the potential for adverse effects. For more aggressive tumors, the dose conformality and normal tissue sparing afforded by IMPT may also allow for dose escalation to target volumes. However, in order to truly maximize the clinical potential of IMPT, the field of radiation oncology must not only implement the most advanced technologies, but also understand and capitalize on the unique biologic aspects of proton therapy.

Journal Title: Neuro-oncology

PUBMED ID: 28373454

DOI: doi.org/10.21873/anticancer.11524

Titolo: A Retrospective Evaluation of Bevacizumab Treatment in Patients with Progressive Malignant Glioma in Northern Sweden.

Autori: Sandström M., Laudius M., Lindqvist T., Asklund T., Johansson M.

Data di Pubblicazione: 2017-4-5

Abstract: Results from this retrospective study are comparable with earlier phase-II studies and motivate randomized trials of bevacizumab-based treatment in the second-line setting.

Journal Title: Anticancer research

PUBMED ID: 28365895

DOI: doi.org/10.1007/s11940-017-0447-4

Titolo: Does Proton Therapy Have a Future in CNS Tumors?

Autori: Combs SE.

Data di Pubblicazione: 2017-4-3

Abstract: Proton therapy is characterized by certain physical properties leading to a reduction in integral dose. As proton therapy becomes more widely available, the ongoing discussion on the real indications for proton therapy becomes more important. In the present article, data on proton therapy for tumors of the central nervous system (CNS) is summarized and discussed in view of modern photon treatments. Still today, no randomized controlled trials are available confirming any clinical benefit of protons in CNS tumors. For certain skull base lesions, such as chordomas and chondrosarcomas, dose escalation is possible with protons thus patients should be referred to a proton center if readily available. For vestibular schwannoma, at present, proton data are inferior to advanced photons. For glioma patients, early data is present for low-grade gliomas, presenting comparable results to photons; dose escalation studies for high-grade gliomas have led to significant side effects, thus strategies of dose-escalation need to be rethought. For skull base meningiomas, data from stereotactic series and IMRT present excellent local control with minimal side effects, thus any improvement with protons might only be marginal. The largest benefit is considered in pediatric CNS tumors, due to the intricate radiation sensitivity of children's normal tissue, as well as the potential of long-term survivorship. Long-term data is still lacking, and even recent analyses do not all lead to a clear reduction in side effect



s with improvement of outcome; furthermore, clinical data seem to be comparable. However, based on the preclinical evidence, proton therapy should be evaluated in every pediatric patient. Protons most likely have a benefit in terms of reduction of long-term side effects, such as neurocognitive sequelae or secondary malignancies; moreover, dose escalation can be performed in radio-resistant histologies. Clinical data with long-term follow-up is still warranted to prove any superiority to advanced photons in CNS tumors. If available, protons should be evaluated for chordoma or chondrosarcoma of the skull base and pediatric tumors. However, many factors are important for excellent oncology care, and no time delay or inferior oncological care should be accepted for the sake of protons only.

Journal Title: Current treatment options in neurology

PUBMED ID: 28347331

DOI: doi.org/10.1186/s40880-017-0201-z

Titolo: Progressive multifocal exophytic pontine glioblastoma: a case report with literature review.

Autori: Chen F., Li Z., Weng C., Li P., Tu L., Chen L., Xie W., Li L.

Data di Pubblicazione: 2017-3-29

Abstract: Multifocal pontine glioblastoma exhibiting an exophytic growth pattern in the cerebello-pontine angle (CPA) is rare. We present a case of a 5-year-old girl with consecutive neurological imaging and other clinical findings indicating progressive multifocal exophytic pontine glioblastoma. Three lesions were reported, of which two were initially presented, and one was developed 2 months later. One lesion demonstrated a progressing exophytic extension in the cistern of the left side of the CPA. The other two lesions were located and confined within the pons. Initial magnetic resonance imaging and positron emission tomography-computed tomography indicated low-grade glioma or inflammatory disease. However, 2 and 3 months later, subsequent magnetic resonance spectroscopy (MRS) displayed elevated choline and depressed N-acetyl aspartate peaks compared with the peaks on the initial MRS, indicating a high-grade glioma. Subtotal resection was performed for the CPA lesion. Histopathologic examination showed discrepant features of different parts of the CPA lesion. The patient received no further chemotherapy or radiotherapy and died 2 months after surgery. The multifocal and exophytic features of this case and the heterogeneous manifestations on neurological images were rare and confusing for both diagnosis and surgical decision-making. Our case report may contribute knowledge and helpful guidance for other medical doctors.

Journal Title: Chinese journal of cancer

PUBMED ID: 28300718

DOI: doi.org/10.1016/j.wneu.2017.03.012

Titolo: Does Pretreatment Tumor Growth Hold Prognostic Information for Patients with Glioblastoma?

Autori: Stensj en AL., Berntsen EM., Mikkelsen VE., Torp SH., Jakola AS., Salvesen  ., Solheim O.

Data di Pubblicazione: 2017-3-17

Abstract: Pretreatment glioblastoma growth harbors prognostic information. Patients with slower growing tumors have higher odds of survival beyond 2 years, adjusted for other prognostic factors.

Journal Title: World neurosurgery

PUBMED ID: 28274399

DOI: doi.org/10.1016/j.prro.2016.11.005

Titolo: Radiation and subsequent reirradiation outcomes in the treatment of diffuse intrinsic pontine glioma and a systematic review of the reirradiation literature.

Autori: Freese C., Takiar V., Fouladi M., DeWire M., Breneman J., Pater L.

Data di Pubblicazione: 2017-3-10

Abstract: Radiation therapy is essential in the definitive management of DIP G. With advances in treatment techniques, it is feasible to reirradiate select patients with progressive disease; however, further research is warranted to optimize dose, delivery, and patient selection in the recurrent/progressive setting. In the future, it may be reasonable to propose more focal delivery of reRT (ie, hypofractionated radiation) in select patients with the goal of reducing treatment time and providing effective palliation.

Journal Title: Practical radiation oncology

PUBMED ID: 28258444

DOI: doi.org/10.1007/s00259-017-3661-0

Titolo: Response assessment of bevacizumab therapy in GBM with integrated 11C-MET-PET/MRI: a feasibility study.

Autori: Deuschl C., Moenninghoff C., Goericke S., Kirchner J., Köppen S., Binse I., Poeppel TD., Quick HH., Forsting M., Umutlu L., Herrmann K., Hense J., Schlamann M.

Data di Pubblicazione: 2017-3-5

Abstract: This study demonstrates the potential of integrated 11C-MET-PET/MRI for response assessment of GBM and the utility of combined assessment of morphologic and metabolic information with the proposal for assessing relapsed GBM.

Journal Title: European journal of nuclear medicine and molecular imaging

PUBMED ID: 31385995

DOI: doi.org/10.1093/nop/npw007

Titolo: Management of primary thalamic low-grade glioma in pediatric patients: results of the multicenter treatment studies HIT-LGG 1996 and SIOP-LGG 2004.

Autori: Boesten T., Gerber NU., Kandels D., Azizi AA., Schmidt R., Warmuth-Metz M., Pietsch T., Kortmann RD., Gnekow A., Grotzer MA.

Data di Pubblicazione: 2019-8-7

Abstract: Thalamic glioma was manageable using a strategy that included surgery, observation, chemotherapy, and/or radiotherapy. Radiotherapy could be successfully deferred or obviated in a number of patients. Survival was high in among patients with monothalamic tumors. The worse prognosis associated with bithalamic tumors correlates with the higher rate of diffuse histology in this subgroup, precluding total or near-total resection.

Journal Title: Neuro-oncology practice

PUBMED ID: 28234741

DOI: doi.org/10.1097/MPH.0000000000000806

Titolo: Concomitant Use of Panobinostat and Reirradiation in Progressive DIPG: Report of 2 Cases.

Autori: Wang ZJ., Ge Y., Altinok D., Poulik J., Sood S., Taub JW., Edwards H., Kieran MW., Steven M.

Data di Pubblicazione: 2017-2-25

Abstract: Diffuse intrinsic pontine glioma (DIPG) remains a devastating disease. Panobinostat has been shown to have therapeutic efficacy both in vitro and in DIPG orthotopic xenograft models; however, clinical data in patients with DIPG are lacking. We present 2 cases of DIPG, who were treated with panobinostat at 22 to 25 mg/m/dose, 3 times weekly for 2 weeks in 3-week cycles and concomitant reirradiation after disease progression. Two episodes of asymptomatic thrombocytopenia were observed in 1 patient. Hyperacetylation of histone H4 of peripheral blood mononuclear cells was evident following treatment.

ent. In our experience, panobinostat administered with reirradiation was well tolerated at a relatively higher dose than that used in adult studies.  
Journal Title: Journal of pediatric hematology/oncology

PUBMED ID: 28228086

DOI: doi.org/10.2174/1568009617666170222125035

Titolo: Clinical Trials with Oncolytic Measles Virus: Current Status and Future Prospects.

Autori: Msaouel P., Opyrchal M., Dispenzieri A., Peng KW., Federspiel MJ., Russell SJ., Galanis E.

Data di Pubblicazione: 2017-2-24

Abstract: Attenuated Edmonston lineage measles virus (MV-Edm) vaccine strains can preferentially infect and lyse a wide variety of cancer cells. Oncolytic MV-Edm derivatives are genetically engineered to express the human carcinoembryonic antigen (MV-CEA virus) or the human sodium iodide symporter (MV-NIS virus) and are currently being tested in clinical trials against ovarian cancer, glioblastoma multiforme, multiple myeloma, mesothelioma, head and neck cancer, breast cancer and malignant peripheral nerve sheath tumors. This review describes the basic and preclinical data that facilitated the clinical translation of MV-Edm strains, and summarizes the clinical results of this oncolytic platform to date. Furthermore, we discuss the latest clinically relevant MV-Edm vector developments and creative strategies for future translational steps.

Journal Title: Current cancer drug targets

PUBMED ID: 28204914

DOI: doi.org/10.1007/s11060-016-2241-7

Titolo: Salvage therapy with bendamustine for temozolomide refractory recurrent anaplastic gliomas: a prospective phase II trial.

Autori: Chamberlain MC., Colman H., Kim BT., Raizer J.

Data di Pubblicazione: 2017-2-17

Abstract: There is no standard therapy for recurrent anaplastic glioma (AG). Salvage therapies include alkylator-based chemotherapy, re-resection with or without carmustine implants, re-irradiation and bevacizumab. Bendamustine is a novel bifunctional alkylator with CNS penetration never previously evaluated in AG. Assess response and toxicity of bendamustine in recurrent AG in a phase II trial. Adults with radiation and temozolomide refractory recurrent AG were treated with bendamustine. A cycle of bendamustine was defined as two consecutive days of treatment (100 mg/m

Journal Title: Journal of neuro-oncology

PUBMED ID: 28204639

DOI: doi.org/10.1093/neuonc/now311

Titolo: Comparison of 2D (RANO) and volumetric methods for assessment of recurrent glioblastoma treated with bevacizumab-a report from the BELOB trial.

Autori: Gahrman R., van den Bent M., van der Holt B., Vernhout RM., Taal W., Vos M., de Groot JC., Beerepoot LV., Buter J., Flach ZH., Hanse M., Jasperse B., Smits M.

Data di Pubblicazione: 2017-2-17

Abstract: In the first 12 weeks, volumetric methods did not provide significant improvement over the RANO criteria as a posttreatment prognostic marker.

Journal Title: Neuro-oncology

PUBMED ID: 28188088

DOI: doi.org/10.1016/j.clon.2017.01.010

Titolo: High-dose Neural Stem Cell Radiation May Not Improve Survival in Glioblastoma.

Autori: Achari R., Arunsingh M., Badgami RK., Saha A., Chatterjee S., Shrima li RK., Mallick I., Arun B.

Data di Pubblicazione: 2017-2-12

Abstract: In this cohort, 67.2% of newly diagnosed glioblastoma patients had NSC involved with CELs at presentation and 95.9% at progression. This might be an imaging surrogate of the current notion of gliomagenesis and progression from NSC rests. A high radiation dose to NSC\_Ipsi was significantly associated with inferior survival. This could be a function of larger tumours and planning target volumes in those with pre-treatment NSC involvement. Methylated MGMT and good compliance to adjuvant temozolomide were independent predictors of better survival. Until further evidence brings hope for glioblastoma, elective, partial NSC irradiation remains experimental.

Journal Title: Clinical oncology (Royal College of Radiologists (Great Britain))

PUBMED ID: 28176936

DOI: doi.org/10.2147/OTT.S125587

Titolo: Add-on bevacizumab can prevent early clinical deterioration and prolong survival in newly diagnosed partially resected glioblastoma patients with a poor performance status.

Autori: Hata N., Yoshimoto K., Hatae R., Kuga D., Akagi Y., Sangatsuda Y., Suzuki SO., Shono T., Mizoguchi M., Iihara K.

Data di Pubblicazione: 2017-2-9

Abstract: Our findings suggest that add-on BEV can prevent early clinical deterioration of pr-GBM patients and contribute to a prolonged survival, especially for those with a poor PS.

Journal Title: OncoTargets and therapy

PUBMED ID: 28176389

DOI: doi.org/10.1111/vru.12474

Titolo: IMAGING DIAGNOSIS -ANTEMORTEM DETECTION OF OLIGODENDROGLIOMA "CEREBROSPINAL FLUID DROP METASTASES" IN A DOG BY SERIAL MAGNETIC RESONANCE IMAGING .

Autori: Vigeral M., Bentley RT., Rancilio NJ., Miller MA., Heng HG.

Data di Pubblicazione: 2017-2-9

Abstract: An English Bulldog underwent radiation therapy of an intracranial, left lateral ventricle mass. Following resolution of the primary mass, an intraventricular fourth ventricle lesion developed. Subsequently, multiple lesions developed from the cervical central canal and leptomeninges. Serial magnetic resonance imaging documented the propagation of lesions along the cerebrospinal fluid (CSF) pathways, known as "CSF drop metastasis." Histopathology confirmed multifocal intraventricular and leptomeningeal oligodendroglioma. Oligodendroglioma should be included in the differential diagnosis for an intraventricular tumor exhibiting apparent CSF drop metastasis.

Journal Title: Veterinary radiology & ultrasound : the official journal of the American College of Veterinary Radiology and the International Veterinary Radiology Association

PUBMED ID: 28169231

DOI: doi.org/10.4103/0973-1482.168988

Titolo: Palbociclib: A new hope in the treatment of breast cancer.

Autori: Palanisamy RP.

Data di Pubblicazione: 2017-2-8

Abstract: Breast cancer being one of the common cancers has high morbidity and mortality. Despite the conventional treatment, the burden of the disease

increases year after year. There is a need for newer drugs that target the different mechanisms in the pathogenesis. The interaction of cyclins with cyclin dependent kinases (CDKs) plays a major role in the abnormal cell cycle in cancer and it is considered to be an important target. Palbociclib is a CDK inhibitor currently approved for the treatment of breast cancer. The preclinical studies with breast cancer lines were sensitive to palbociclib and the clinical trials phase I, phase II (PALOMA 1), and phase III (PALOMA 2, 3, PENTELOPE, PEARL) showed that the drug was efficacious when combined with other conventional drugs for breast cancer. Palbociclib was also been tested in various other germ cell tumors, melanoma, multiple myeloma, glioblastoma multiforme etc., The major adverse effect of the drug includes hematological toxicity mainly neutropenia, gastrointestinal adverse effects.  
Journal Title: Journal of cancer research and therapeutics

PUBMED ID: 28161497

DOI: doi.org/10.1016/j.ejca.2016.12.007

Titolo: Survival benefit for patients with diffuse intrinsic pontine glioma (DIPG) undergoing re-irradiation at first progression: A matched-cohort analysis on behalf of the SIOP-E-HGG/DIPG working group.

Autori: Janssens GO., Gandola L., Bolle S., Mandeville H., Ramos-Albiac M., van Beek K., Benghiat H., Hoeben B., Morales La Madrid A., Kortmann RD., Hargrave D., Menten J., Pecori E., Biassoni V., von Bueren AO., van Vuurden DG., Massimino M., Sturm D., Peters M., Kramm CM.

Data di Pubblicazione: 2017-2-6

Abstract: The majority of patients with DIPG, responding to upfront radiotherapy, do benefit of re-irradiation with acceptable tolerability.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 28123740

DOI: doi.org/10.3892/mco.2016.1086

Titolo: Efficacy of bevacizumab therapy for unresectable malignant glioma: A retrospective analysis.

Autori: Yonezawa H., Hirano H., Uchida H., Habu M., Hanaya R., Oyoshi T., Sadamura Y., Hanada T., Tokimura H., Moinuddin F., Arita K.

Data di Pubblicazione: 2017-1-27

Abstract: Bevacizumab (BEV), an inhibitor of vascular endothelial growth factor A, has been used for primary and recurrent malignant gliomas in Japan since June, 2013. Previous randomized controlled studies demonstrated that BEV prolonged the progression-free survival, but not the overall survival (OS) of patients with newly diagnosed glioblastoma. The aim of the present study was to elucidate the effect of BEV on the OS of patients with unresectable malignant gliomas. Of the 440 cases of malignant glioma initially treated in our institute between 2000 and 2015, 88 were not suitable for maximal resection due to patient age, physical condition, tumor location and extent, or the patient's wishes. Based on the biopsy results, the pathological diagnosis was glioblastoma, anaplastic astrocytoma and anaplastic oligodendroglioma in 60, 19 and 9 patients, respectively. Kaplan-Meier and log-rank analyses were performed to investigate the effect of BEV on OS. OS was longer in the BEV group (n=24) compared with that in the non-BEV group [n=64; median survival time (MST), 566 vs. 243 days, respectively; hazard ratio (HR)=0.413; 95% confidence interval (CI): 0.216-0.787; P=0.003]. In the 41 patients who received temozolomide (TMZ) and radiotherapy and the 31 patients with glioblastoma who received TMZ and radiotherapy, OS was longer in the BEV group compared with that in the non-BEV group (MST, 568 vs. 334 days, HR=0.404, 95% CI: 0.175-0.933, P=0.016; and MST, 566 vs. 160 days, HR=0.253, 95% CI: 0.099-0.646, P=0.001, respectively). In the Cox hazard model analysis of 41 patients who underwent TMZ-based chemoradiotherapy after biopsy, the use of BEV was the strongest independent beneficial factor associated with prolonged OS (HR=0.101;

P=0.0002). Our retrospective survey suggested that BEV prolongs the OS of patients with unresectable malignant gliomas. However, these results must be verified by a well-designed prospective randomized controlled trial.

Journal Title: Molecular and clinical oncology

PUBMED ID: 28110346

DOI: doi.org/10.1007/s00259-017-3618-3

Titolo: Prognostic value of molecular and imaging biomarkers in patients with supratentorial glioma.

Autori: Lopci E., Riva M., Olivari L., Raneri F., Soffietti R., Piccardo A., Bizzi A., Navarria P., Ascolese AM., Rudà R., Fernandes B., Pessina F., Grimaldi M., Simonelli M., Rossi M., Alfieri T., Zucali PA., Scorsetti M., Bello L., Chiti A.

Data di Pubblicazione: 2017-1-23

Abstract: None

Journal Title: European journal of nuclear medicine and molecular imaging

PUBMED ID: 28084680

DOI: doi.org/10.1002/pbc.26416

Titolo: Rapid and fulminant leptomeningeal spread following radiotherapy in diffuse intrinsic pontine glioma.

Autori: Tinkle CL., Orr BA., Lucas JT., Klimo P., Patay Z., Baker SJ., Broniscer A., Qaddoumi I.

Data di Pubblicazione: 2017-1-14

Abstract: A 4-year-old male presented with rapid-onset cranial nerve palsy and ataxia. Brain magnetic resonance imaging (MRI) revealed a pontine mass lesion with discordant conventional and advanced imaging. A stereotactic core biopsy revealed glioblastoma with immunostaining suggestive of histone H3K27M and TP53 mutation, consistent with diffuse intrinsic pontine glioma. MRI 3 months after radiotherapy revealed extensive new leptomeningeal metastatic disease involving both the supra- and infratentorial brain, as well as the imaged portion of the spine. Tissue procured at the time of needle biopsy has undergone striking in vivo expansion as an orthotopic xenograft.

Journal Title: Pediatric blood & cancer

PUBMED ID: 28070598

DOI: doi.org/10.1007/s00234-016-1769-8

Titolo: Advanced MRI assessment to predict benefit of anti-programmed cell death 1 protein immunotherapy response in patients with recurrent glioblastoma.

Autori: Qin L., Li X., Stroiney A., Qu J., Helgager J., Reardon DA., Young GS.

Data di Pubblicazione: 2017-1-11

Abstract: MRI reveals an initial increase in volumes of abnormal tissue with contrast enhancement, edema, and intermediate ADC suggesting hypercellularity within the first 0-6 months of immunotherapy. Subsequent stabilization and improvement in IADC VOI appear to better predict ultimate therapeutic benefit from these agents than conventional imaging.

Journal Title: Neuroradiology

PUBMED ID: 28052119

DOI: doi.org/10.1371/journal.pone.0169485

Titolo: Pre-Clinical Study of Panobinostat in Xenograft and Genetically Engineered Murine Diffuse Intrinsic Pontine Glioma Models.

Autori: Hennika T., Hu G., Olaciregui NG., Barton KL., Ehteda A., Chitrnanjan A., Chang C., Gifford AJ., Tsoi M., Ziegler DS., Carcaboso AM., Becher OJ.

Data di Pubblicazione: 2017-1-5

Abstract: Our collaborative pre-clinical study confirms that panobinostat is an effective targeted agent against DIPG human and murine tumor cells in vitro and in short-term in vivo efficacy studies in mice but does not significantly impact survival of mice bearing H3.3-K27M-mutant tumors. We suggest this may be due to toxicity associated with systemic administration of panobinostat that necessitated dose de-escalation.

Journal Title: PloS one

PUBMED ID: 28049229

DOI: doi.org/10.3346/jkms.2017.32.2.195

Titolo: Tandem High-Dose Chemotherapy and Autologous Stem Cell Transplantation for High-Grade Gliomas in Children and Adolescents.

Autori: Lee JW., Lim DH., Sung KW., Lee HJ., Yi ES., Yoo KH., Koo HH., Suh Y L., Shin HJ.

Data di Pubblicazione: 2017-1-4

Abstract: With the aim to investigate the outcome of tandem high-dose chemotherapy and autologous stem cell transplantation (HDCT/auto-SCT) for high-grade gliomas (HGGs), we retrospectively reviewed the medical records of 30 patients with HGGs (16 glioblastomas, 7 anaplastic astrocytomas, and 7 other HGGs) between 2006 and 2015. Gross or near total resection was possible in 11 patients. Front-line treatment after surgery was radiotherapy (RT) in 14 patients and chemotherapy in the remaining 16 patients including 3 patients less than 3 years of age. Eight of 12 patients who remained progression free and 5 of the remaining 18 patients who experienced progression during induction treatment underwent the first HDCT/auto-SCT with carboplatin + thiotepa + etoposide (CTE) regimen and 11 of them proceeded to the second HDCT/auto-SCT with cyclophosphamide + melphalan (CyM) regimen. One patient died from hepatic veno-occlusive disease (VOD) during the second HDCT/auto-SCT; otherwise, toxicities were manageable. Four patients in complete response (CR) and 3 of 7 patients in partial response (PR) or second PR at the first HDCT/auto-SCT remained event free: however, 2 patients with progressive tumor experienced progression again. The probabilities of 3-year overall survival (OS) after the first HDCT/auto-SCT in 11 patients in CR, PR, or second PR was  $58.2\% \pm 16.9\%$ . Tumor status at the first HDCT/auto-SCT was the only significant factor for outcome after HDCT/auto-SCT. There was no difference in survival between glioblastoma and other HGGs. This study suggests that the outcome of HGGs in children and adolescents after HDCT/auto-SCT is encouraging if the patient could achieve CR or PR before HDCT/auto-SCT.

Journal Title: Journal of Korean medical science

PUBMED ID: 28025828

DOI: doi.org/10.1111/ane.12719

Titolo: Prognostic parameters and outcome after re-irradiation for progressive glioblastoma.

Autori: Zwirner K., Paulsen F., Schittenhelm J., Borchers C., Skardelly M., Zips D., Eckert F.

Data di Pubblicazione: 2016-12-28

Abstract: The favourable results regarding overall survival are probably due to patient selection for re-irradiation. If technically feasible, stereotactic radiosurgery or hypofractionated regimes should be preferred. In this highly selected re-irradiation cohort, only some of the well-known prognostic factors of the primary tumour setting were found to influence overall survival significantly. In contrast, also some patients presenting with unfavourable predictive parameters showed an encouraging course of disease and thus should not be excluded from re-irradiation.

Journal Title: Acta neurologica Scandinavica

PUBMED ID: 28019637

DOI: doi.org/10.2174/0929867323666161223150242

Titolo: Recent Advances in Targeted Therapy for Glioma.

Autori: Lin L., Cai J., Jiang C.

Data di Pubblicazione: 2016-12-27

Abstract: Gliomas are the most common primary malignant brain tumors, which have a universally fatal outcome. Current standard treatment for glioma patients is surgical removal followed by radiotherapy and adjuvant chemotherapy. Due to therapeutic resistance and tumor recurrence, efforts are ongoing to identify the molecules that are fundamental to regulate the tumor progression and provide additional methods for individual treatment of glioma patients. By studying the initiation and maintenance of glioma, studies focused on the targets of tyrosine kinase receptors including EGFR, PDGFR and other crucial signal pathways such as PI3K/AKT and RAS/RAF/MAPK pathway. Furthermore, recent advances in targeting immunotherapy and stem cell therapy also brought numerous strategies to glioma treatment. This article reviewed the researches focused on the advanced strategies of various target therapies for improving the glioma treatment efficacy, and discussed the challenges and future directions for glioma therapy.

Journal Title: Current medicinal chemistry

PUBMED ID: 28009226

DOI: doi.org/10.3171/2016.9.PEDS16328

Titolo: Report of effective trametinib therapy in 2 children with progressive hypothalamic optic pathway pilocytic astrocytoma: documentation of volumetric response.

Autori: Miller C., Guillaume D., Dusenbery K., Clark HB., Moertel C.

Data di Pubblicazione: 2016-12-24

Abstract: Brain tumors are the most common solid tumor in childhood, and astrocytomas account for the largest proportion of these tumors. Increasing sophistication in genetic testing has allowed for the detection of specific mutations within tumor subtypes that may represent targets for individualized tumor treatment. The mitogen-activating protein kinase (MAPK) pathway and, more specifically, BRAF mutations have been shown to be prevalent in pediatric pilocytic astrocytomas and may represent one such area to target. Herein, the authors describe 2 cases of inoperable, chemotherapy-resistant pediatric pilocytic astrocytomas with a documented response to trametinib, an MAPK pathway inhibitor. While these cases were not treated in the setting of a clinical trial, their data support further ongoing clinical trial investigation to evaluate the safety and efficacy of this agent in pediatric low-grade gliomas.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 27998280

DOI: doi.org/10.1186/s12987-016-0047-9

Titolo: Misleading early blood volume changes obtained using ferumoxytol-based magnetic resonance imaging perfusion in high grade glial neoplasms treated with bevacizumab.

Autori: Netto JP., Schwartz D., Varallyay C., Fu R., Hamilton B., Neuwelt EA.

Data di Pubblicazione: 2016-12-22

Abstract: Decreased perfusion after BEV significantly alters rCBV measurements when using ferumoxytol. BEV treatment response hinders efforts to differentiate true progression from pseudoprogression using blood volume measurements in malignant glioma, potentially impacting patient diagnosis and management.

Journal Title: Fluids and barriers of the CNS



PUBMED ID: 27921166

DOI: doi.org/10.1007/s00415-016-8355-1

Titolo: Outcome in unresectable glioblastoma: MGMT promoter methylation makes the difference.

Autori: Thon N., Thorsteinsdottir J., Eigenbrod S., Schüller U., Lutz J., Kreth S., Belka C., Tonn JC., Niyazi M., Kreth FW.

Data di Pubblicazione: 2016-12-7

Abstract: In 2011, we reported a predominant prognostic/predictive role of MGMT promoter methylation status on progression-free survival (PFS) in unresectable glioblastoma patients undergoing upfront radiotherapy plus concomitant and maintenance temozolomide (RTX/TMZ → TMZ). We, here, present the final results of this prospective study focussing on the prognostic/predictive value of MGMT promoter methylation status for death risk stratification. Overall, 56 adult patients with unresectable, biopsy proven glioblastoma were prospectively assigned to upfront RTX/TMZ → TMZ treatment between March 2006 and August 2008. Last follow-up was performed in June 2016. MGMT promoter methylation was determined using methylation-specific PCR (MSP) and sodium bisulfite sequencing. Analyses were done by intention to treat. Prognostic factors were obtained from proportional hazard models. At the time of the final analysis 55 patients showed progressive disease and 53 patients had died. MGMT promoter was methylated (unmethylated) in 30 (26) patients. Methylation of the MGMT promoter was the strongest favorable predictor for overall survival (OS, median: 20.3 vs. 7.3 months,  $p < 0.001$ , HR 0.30, 95% CI 0.16-0.55), and PFS (median: 15.0 vs. 6.1 months,  $p < 0.001$ , HR 0.31, 95% CI 0.17-0.57) and was also associated with higher frequencies of treatment response and prolonged post-recurrence survival (PRS, median: 4.5 vs. 1.4 months,  $p < 0.002$ , HR 0.39, 95% CI 0.21-0.71). Knowledge of MGMT promoter methylation status is essential for patients' counseling, prognostic evaluation, and for the design of future trials dealing with unresectable glioblastomas.

Journal Title: Journal of neurology

PUBMED ID: 27893017

DOI: doi.org/10.1001/jamaneurol.2016.4226

Titolo: Evaluation of Cognitive Deficits and Structural Hippocampal Damage in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 Antibodies.

Autori: Finke C., Prüss H., Heine J., Reuter S., Kopp UA., Wegner F., Thoenen F., Koch S., Jansen O., Münte T., Deuschl G., Rupprecht K., Stöcker W., Wandinger KP., Paul F., Bartsch T.

Data di Pubblicazione: 2016-11-29

Abstract: Anti-LGI1 encephalitis is associated with cognitive deficits and disability as a result of structural damage to the hippocampal memory system. This damage might be prevented by early immunotherapy.

Journal Title: JAMA neurology

PUBMED ID: 27853960

DOI: doi.org/10.1007/s11060-016-2332-5

Titolo: Phase II study of tivozanib, an oral VEGFR inhibitor, in patients with recurrent glioblastoma.

Autori: Kalpathy-Cramer J., Chandra V., Da X., Ou Y., Emblem KE., Muzikansky A., Cai X., Douw L., Evans JG., Dietrich J., Chi AS., Wen PY., Stufflebeam S., Rosen B., Duda DG., Jain RK., Batchelor TT., Gerstner ER.

Data di Pubblicazione: 2016-11-18

Abstract: Targeting tumor angiogenesis is a potential therapeutic strategy for glioblastoma because of its high vascularization. Tivozanib is an oral pan-VEGF receptor tyrosine kinase inhibitor that hits a central pathway in glioblastoma angiogenesis. We conducted a phase II study to test the effectiveness

ess of tivozanib in patients with recurrent glioblastoma. Ten adult patients were enrolled and treated with tivozanib 1.5 mg daily, 3 weeks on/1 week off in 28-day cycles. Brain MRI and blood biomarkers of angiogenesis were performed at baseline, within 24-72 h of treatment initiation, and monthly thereafter. Dynamic contrast enhanced MRI, dynamic susceptibility contrast MRI, and vessel architecture imaging were used to assess vascular effects. Resting state MRI was used to assess brain connectivity. Best RANO criteria responses were: 1 complete response, 1 partial response, 4 stable diseases, and 4 progressive disease (PD). Two patients were taken off study for toxicity and 8 patients were taken off study for PD. Median progression-free survival was 2.3 months and median overall survival was 8.1 months. Baseline abnormal tumor vascular permeability, blood flow, tissue oxygenation and plasma sVEGFR2 significantly decreased and plasma PlGF and VEGF increased after treatment, suggesting an anti-angiogenic effect of tivozanib. However, there were no clear structural changes in vasculature as vessel caliber and enhancing tumor volume did not significantly change. Despite functional changes in tumor vasculature, tivozanib had limited anti-tumor activity, highlighting the limitations of anti-VEGF monotherapy. Future studies in glioblastoma should leverage the anti-vascular activity of agents targeting VEGF to enhance the activity of other therapies.

Journal Title: Journal of neuro-oncology

PUBMED ID: 27844308

DOI: doi.org/10.1007/s11060-016-2331-6

Titolo: Impact of concurrent chemotherapy with radiation therapy for elderly patients with newly diagnosed glioblastoma: a review of the National Cancer Data Base.

Autori: Huang J., Samson P., Perkins SM., Ansstas G., Chheda MG., DeWees TA., Tsien CI., Robinson CG., Campian JL.

Data di Pubblicazione: 2016-11-16

Abstract: To investigate the utilization and overall survival (OS) impact of concurrent chemotherapy in combination with radiation therapy (RT) for elderly glioblastoma (GBM) patients. Elderly patients (age >70) with supratentorial and nonmetastatic GBM who received RT of 20-75 Gy with concurrent single-agent chemotherapy (ChemoRT) or without (RT alone) during 2004-2012 were identified from the National Cancer Data Base (NCDB). The Cochran-Armitage test was used for trend analysis. Hazard ratios (HR) and 95% confidence intervals (CIs) were determined using Cox proportional hazards. Propensity score analysis was performed to reduce selection bias in treatment allocation. A total of 5252 patients were identified (RT alone: n=1389; ChemoRT: n=3863). There was increasing utilization of chemotherapy during this period (45-80%,  $P<.001$ ). A similar trend was also observed for the subset of age >80 (25-68%,  $P<.001$ ). ChemoRT was associated with significantly better OS than RT alone (HR 0.79, 95% CI 0.70-0.89,  $P<.001$ ) on multivariate analysis, and similar OS benefit was demonstrated with 1202 pairs of propensity-matched patients (HR 0.79, 95% CI 0.73-0.86,  $P<.001$ ). For the matched pair, the median OS was 5.8 months with ChemoRT and 5.0 months with RT alone; the 2-year OS rate was 9% with ChemoRT and 4% with RT alone ( $P<.001$ ). Concurrent chemotherapy has been administered with RT for the majority of elderly GBM patients. Addition of chemotherapy to RT for elderly GBM patients is associated with significantly improve OS in routine clinical practice.

Journal Title: Journal of neuro-oncology

PUBMED ID: 27840944

DOI: doi.org/10.3892/mmr.2016.5921

Titolo: Dec1 expression predicts prognosis and the response to temozolomide chemotherapy in patients with glioma.

Autori: Li XM., Lin W., Wang J., Zhang W., Yin AA., Huang Y., Zhang J., Yao L., Bian H., Zhang J., Zhang X.

Data di Pubblicazione: 2016-11-15

Abstract: Differentiated embryo chondrocyte expressed gene 1 (Dec1), a crucial cell differentiation mediator and apoptosis inhibitor, is abundantly expressed in various types of human cancer and is associated with malignant tumor progression. As poor differentiation and low apoptosis are closely associated with poor survival rates and a poor response to radio/chemotherapy in patients with cancer, the prognostic value of Dec1 expression was examined in the present study and its correlation with response to temozolomide (TMZ) chemotherapy was analyzed in patients with glioma. Dec1 expression was analyzed by immunohistochemistry in 157 samples of newly diagnosed glioma and 63 recurrent glioblastoma cases that relapsed during TMZ chemotherapy. Correlations with clinical variables, prognosis and the response to TMZ chemotherapy were analyzed in the newly diagnosed gliomas. Dec1 expression was also compared with the apoptosis index determined by TdT-mediated dUTP nick ending-labeling assay in recurrent glioblastomas. The antiglioma effect of TMZ in nude mice xenografts with Dec1 expression was examined in vivo. High expression of Dec1, which was significantly associated with high pathological tumor grade and poor response to TMZ chemotherapy, was demonstrated to be an unfavorable independent prognostic factor and predicted poor survival in patients with newly diagnosed glioma. In patients with recurrent glioblastoma, there was a negative correlation between Dec1 expression and the apoptotic index. In nude mice treated with TMZ, Dec1 overexpression potentiated proliferation, but attenuated TMZ-induced apoptosis. In conclusion, Dec1 is a prognostic factor for the clinical outcome and a predictive factor for the response to TMZ chemotherapy in patients with glioma.

Journal Title: Molecular medicine reports

PUBMED ID: 27826681

DOI: doi.org/10.1007/s11060-016-2310-y

Titolo: Role of surgical resection in recurrent glioblastoma: prognostic factors and outcome evaluation in an observational study.

Autori: Pessina F., Navarria P., Cozzi L., Tomatis S., Riva M., Ascolese AM., Santoro A., Simonelli M., Bello L., Scorsetti M.

Data di Pubblicazione: 2016-11-10

Abstract: The role of surgical resection in progressive or recurrent glioblastoma multiforme (GBM) lack of high level of evidence. The aim of this evaluation was to assess the role of surgical resection in relapsing GBM, in relation to the extent of surgical resection (EOR) and the amount of residual tumor volume (RTV). Among patients treated for newly diagnosed GBM between September 2008-December 2014, 64 patients with recurrent GBM were included in this retrospective evaluation. All patients underwent surgical resection followed by adjuvant treatments, chemotherapy and/or radiotherapy. Results were evaluated in terms of local control (LC) rate, progression free survival (PFS) and patients overall survival (OS). Gross total resection (GTR) (>90%) was achieved in 48 (75%) patients and subtotal resection (STR) in 16 (25%). RTV was 0 in 40 (62.5%) patients and >0 in 24 (37.5%). No severe postoperative morbidity occurred. The median LC time was  $6.0 \pm 0.1$  months (95% CI 5.29-8.55), with a 1 and 2 years LC rate of  $29.4 \pm 6.9\%$ . The median PFS time was  $6.8 \pm 0.8$  months, with a 1 year PFS rate of  $27.2 \pm 7.2\%$  (95% CI 14.2-41.9). The median OS time was  $10.3 \pm 0.5$  months (95% CI 7.6-10.4) with a 1 and 2 years OS rate of  $22.5 \pm 6.7\%$  (95% CI 10.9-36.6). On univariate analysis EOR and RTV were recorded as conditioning LC and survival. These data was confirmed also in multivariate analysis only for RTV ( $p < 0.01$ ). Recurrent GBM can take advantage of repeated surgery in selected patients with younger age and good clinical status. The entity of surgical resection was confirmed as conditioning survival.

Journal Title: Journal of neuro-oncology

PUBMED ID: 27811370

DOI: doi.org/10.18632/oncotarget.13028

Titolo: IL-10 and PRKDC polymorphisms are associated with glioma patient survival.

Autori: Hu M., Du J., Cui L., Huang T., Guo X., Zhao Y., Ma X., Jin T., Li G., Song J.

Data di Pubblicazione: 2016-11-5

Abstract: Interleukin-10 (IL-10) and DNA repair gene PRKDC mutations are implicated in the development of multiple human cancers, including glioma. We investigated associations between IL-10 and PRKDC gene polymorphisms and prognosis in low- and high-grade glioma patients. We analyzed the associations of one IL-10 and one PRKDC single nucleotide polymorphism with patient clinical factors in 481 glioma patients using Cox proportional hazard models and Kaplan-Meier curves. We also assessed associations between patient clinical characteristics and prognosis. Our data showed that the extent of tumor resection (gross-total resection) and application of chemotherapy were associated with improved patient outcomes in all glioma cases. Additionally, univariate (Log-rank  $p = 0.019$ ) and multivariate Cox regression analyses ( $p = 0.022$ ) showed that the IL-10 rs1800871 C/T genotype correlates with improved overall survival in cases of low-grade glioma, whereas the PRKDC rs7003908 C/C genotype correlated with reduced overall and progression-free survival in high-grade glioma patients in univariate (Log-rank  $p = 0.000$  and  $p = 0.000$ , respectively) and multivariate Cox regression analyses ( $p = 0.001$ ;  $p = 0.002$ , respectively). These results suggest that IL-10 rs1800871 and PRKDC rs7003908 may be useful biomarkers for predicting glioma patient outcome. Further functional studies are needed to evaluate the mechanisms by which these polymorphisms affect glioma progression.

Journal Title: Oncotarget

PUBMED ID: 27810966

DOI: doi.org/10.1177/0883073816675547

Titolo: Brainstem Low-Grade Gliomas in Children-Excellent Outcomes With Multimodality Therapy.

Autori: Upadhyaya SA., Koschmann C., Muraszko K., Venneti S., Garton HJ., Hamstra DA., Maher CO., Betz BL., Brown NA., Wahl D., Weigelin HC., DuRoss KE., Leonard AS., Robertson PL.

Data di Pubblicazione: 2016-11-5

Abstract: Safe maximal surgical resection is the initial treatment of choice for pediatric brainstem low-grade gliomas. Optimal therapy for incompletely resected tumors or that progress after surgery is uncertain. We reviewed the clinical characteristics, therapy, and outcomes of all children with nonsectal brainstem low-grade gliomas treated at the University of Michigan between 1993 and 2013. Median age at diagnosis was 6 years; histology was confirmed in 23 of 25 tumors, 64% were pilocytic astrocytoma. Nineteen patients underwent initial tumor resection; 14/19 received no upfront adjuvant therapy. Eight patients in the study had progressive disease; 5 initially resected tumors received chemotherapy at tumor relapse, all with partial or complete radiographic responses. Ten-year progression-free survival is 71% and overall survival, 100%. This single-institution retrospective study demonstrates excellent survival rates for children with brainstem low-grade gliomas. The efficacy of the well-tolerated chemotherapy in this series supports its role in the treatment of unresectable or progressive brainstem low-grade gliomas.

Journal Title: Journal of child neurology

PUBMED ID: 27809808

DOI: doi.org/10.1186/s12885-016-2890-0

Titolo: Planning TTFIELDS treatment using the NovoTAL system-clinical case series beyond the use of MRI contrast enhancement.

Autori: Connelly J., Hormigo A., Mohile N., Hu J., Chaudhry A., Blondin N.

Data di Pubblicazione: 2016-11-5

Abstract: This paper details important approaches for integrating clinical considerations, nonmeasurable disease and advanced imaging into the treatment planning workflow for TTFIELDS. As TTFIELDS become integrated into standard care pathways for glioblastoma, this case series demonstrates that treatment planning beyond the extent of contrast enhancement is clinically feasible and should be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

Journal Title: BMC cancer

PUBMED ID: 27693428

DOI: doi.org/10.1016/j.jconrel.2016.09.034

Titolo: Anticancer drug-loaded hydrogels as drug delivery systems for the local treatment of glioblastoma.

Autori: Bastiancich C., Danhier P., Préat V., Danhier F.

Data di Pubblicazione: 2016-11-7

Abstract: Among central nervous system tumors, Glioblastoma (GBM) is the most common, aggressive and neurological destructive primary brain tumor in adults. Standard care therapy for GBM consists in surgical resection of the accessible tumor (without causing neurological damage) followed by chemoradiation. However, several obstacles limit the assessment of tumor response and the delivery of cytotoxic agents at the tumor site, leading to a lack of effectiveness of conventional treatments against GBM and fatal outcome. Despite the efforts of the scientific community to increase the long-term benefits of GBM therapy, at the moment GBM remains incurable. Among the strategies that have been adopted in the last two decades to find new and efficacious therapies for the treatment of GBM, the local delivery of chemotherapeutic drugs in the tumor resection cavity emerged. In this review, our aim is to provide an overview on hydrogels loaded with anticancer drugs for the treatment of GBM recently used in preclinical and clinical studies, their advantages and major limitations for clinical translation. This review is divided in three parts: the first one describes the context of GBM and its current treatments, with a highlight on the role of local delivery in GBM treatment and the development of GBM resection murine models. Then, recent developments in the use of anticancer drug-loaded hydrogels for the treatment of GBM will be detailed. The final section will be focused on the limitations for in vivo studies, clinical translation and the clinical perspectives to the development of hydrogels.

Journal Title: Journal of controlled release : official journal of the Controlled Release Society

PUBMED ID: 27744717

DOI: doi.org/10.1080/14712598.2016.1249846

Titolo: The prospect of patritumab for treating non-small cell lung cancer.

Autori: Horinouchi H.

Data di Pubblicazione: 2016-10-18

Abstract: The mutation or expression of HER family members serves as a therapeutic target for tyrosine kinase inhibitors or monoclonal antibodies in diverse cancers, such as non-small cell lung cancer, breast cancer, gastric cancer, head and neck cancer, colorectal cancer, pancreatic cancer and glioblastoma. HER3, which heterodimerizes with HER1 and HER2, has received much attention as a potential target for anti-EGFR treatment. Patritumab is a novel, fully human monoclonal antibody directed against HER3. Areas covered: In this review article, an overview of the market, chemistry, pharmacodynamics, ph

armacokinetics, efficacy, and safety of patritumab is provided based on data from phase I studies, a combination phase I trial, and a randomized phase II trial comparing two doses of patritumab. Expert opinion: The combination of patritumab plus erlotinib has shown a promising efficacy and safety in early-phase clinical trials. In a randomized phase II trial, higher mRNA expression of heregulin (a ligand of HER3) was associated with better progression-free survival and a tendency toward improved overall survival. In the era of precise treatment based on an appropriate target with a predictive biomarker, further studies with patritumab are needed to realize its potential in cancer treatment.

Journal Title: Expert opinion on biological therapy

PUBMED ID: 27796446

DOI: doi.org/10.1007/s00234-016-1741-7

Titolo: Prognostic value of preoperative dynamic contrast-enhanced MRI perfusion parameters for high-grade glioma patients.

Autori: Ulyte A., Katsaros VK., Liouta E., Stranjalis G., Boskos C., Papanikolaou N., Usinskiene J., Bisdas S.

Data di Pubblicazione: 2016-11-1

Abstract: High v

Journal Title: Neuroradiology

PUBMED ID: 27645758

DOI: doi.org/10.5692/clinicalneurology-000928

Titolo: A case of progressive multifocal leukoencephalopathy with chronic renal failure, whose JC virus in cerebrospinal fluid disappeared after mefloquine-mirtazapine dual therapy.

Autori: Ohnuki E., Asayama S., Asayama T., Nakamichi K., Saijo M., Kosaka S.

Data di Pubblicazione: 2016-9-21

Abstract: An 83-year-old man with chronic renal failure was referred to our hospital because of subacute progressive right hemiparesis. A brain MRI showed high-intensity lesions in bilateral middle cerebellar peduncles and white matter of the left frontal lobe on T

Journal Title: Rinsho shinkeigaku = Clinical neurology

PUBMED ID: 26558632

DOI: doi.org/10.1007/s12035-015-9525-3

Titolo: Proliferating Cell Nuclear Antigen Has an Association with Prognosis and Risks Factors of Cancer Patients: a Systematic Review.

Autori: Lv Q., Zhang J., Yi Y., Huang Y., Wang Y., Wang Y., Zhang W.

Data di Pubblicazione: 2015-11-13

Abstract: Proliferating cell nuclear antigen (PCNA) is reported as a famous marker in various tumors. A couple of articles have been published about the clinical function of PCNA on cancer progression; however, these results are conflicting in some degree. Thus, it is crucial to perform a systematic review and meta-analysis to identify their real actions. Here, we took cervical cancer and glioma as example and then pooled hazard ratios (HRs) or odds ratios (ORs) with 95 % confidence intervals (95 % CIs). In the present study, the PCNA expression in cervical cancer and gliomas patients was both correlated with 5-year-overall survival (OS) (HR=4.41, 95 % CI 2.71-7.17, p=0.000; HR=4.40, 95 % CI 3.00-6.47, p=0.000; respectively). In addition, a fixed effect model revealed a significant association between PCNA and FIGO stage (OR=4.48, 95 % CI 3.48-5.77, p=0.000) or WHO grade (OR=5.64, 95 % CI 4.15-7.68, p=0.000), rather than age (OR=1.01, 95 % CI 0.71-1.43, p=0.957; OR=1.00, 95 % CI 0.80-1.24, p=0.989; respectively). No heterogeneity was observed across all studies. According to funnel plot, no publication bias was reported.

ed. In conclusion, our systematic review suggests that PCNA expression is significantly associated with poor 5-year survival, advanced stage or higher WHO grade, which might be suggested as a useful prognostic and diagnostic biomarker, or an effective therapy target in cervical cancer, gliomas, or even more cancers.

Journal Title: Molecular neurobiology

PUBMED ID: 27486853

DOI: doi.org/10.1111/cas.13027

Titolo: Oncolytic virus therapy: A new era of cancer treatment at dawn.

Autori: Fukuhara H., Ino Y., Todo T.

Data di Pubblicazione: 2016-8-4

Abstract: Oncolytic virus therapy is perhaps the next major breakthrough in cancer treatment following the success in immunotherapy using immune checkpoint inhibitors. Oncolytic viruses are defined as genetically engineered or naturally occurring viruses that selectively replicate in and kill cancer cells without harming the normal tissues. T-Vec (talimogene laherparepvec), a second-generation oncolytic herpes simplex virus type 1 (HSV-1) armed with GM-CSF, was recently approved as the first oncolytic virus drug in the USA and Europe. The phase III trial proved that local intralesional injections with T-Vec in advanced malignant melanoma patients can not only suppress the growth of injected tumors but also act systemically and prolong overall survival. Other oncolytic viruses that are closing in on drug approval in North America and Europe include vaccinia virus JX-594 (pexastimogene devacirepvec) for hepatocellular carcinoma, GM-CSF-expressing adenovirus CG0070 for bladder cancer, and Reolysin (pelareorep), a wild-type variant of reovirus, for head and neck cancer. In Japan, a phase II clinical trial of G47 $\Delta$ , a third-generation oncolytic HSV-1, is ongoing in glioblastoma patients. G47 $\Delta$  was recently designated as a "Sakigake" breakthrough therapy drug in Japan. This new system by the Japanese government should provide G47 $\Delta$  with priority reviews and a fast-track drug approval by the regulatory authorities. Whereas numerous oncolytic viruses have been subjected to clinical trials, the common feature that is expected to play a major role in prolonging the survival of cancer patients is an induction of specific antitumor immunity in the course of tumor-specific viral replication. It appears that it will not be long before oncolytic virus therapy becomes a standard therapeutic option for all cancer patients.

Journal Title: Cancer science

PUBMED ID: 27334276

DOI: doi.org/10.1007/s00066-016-1007-7

Titolo: Intensity-modulated proton therapy, volumetric-modulated arc therapy, and 3D conformal radiotherapy in anaplastic astrocytoma and glioblastoma: A dosimetric comparison.

Autori: Adeberg S., Harrabi SB., Bougatf N., Bernhardt D., Rieber J., Koerber SA., Syed M., Sprave T., Mohr A., Abdollahi A., Haberer T., Combs SE., Herfarth K., Debus J., Rieken S.

Data di Pubblicazione: 2016-6-24

Abstract: Essential dose reduction while maintaining equal target volume coverage was observed using PRT, particularly in contralaterally located critical neuronal structures, areas of neurogenesis, and structures of neurocognitive functions. These findings were supported by preliminary clinical results confirming the safety and feasibility of PRT in HGG.

Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 27770279

DOI: doi.org/10.1007/s11060-016-2288-5

Titolo: NRG oncology RTOG 0625: a randomized phase II trial of bevacizumab with either irinotecan or dose-dense temozolomide in recurrent glioblastoma.

Autori: Gilbert MR., Pugh SL., Aldape K., Sorensen AG., Mikkelsen T., Penas-Prado M., Bokstein F., Kwok Y., Lee RJ., Mehta M.

Data di Pubblicazione: 2016-10-23

Abstract: Angiogenesis, a hallmark of glioblastoma, can potentially be targeted by inhibiting the VEGF pathway using bevacizumab, a humanized monoclonal antibody against VEGF-A. This study was designed to determine the efficacy and safety of these regimens in the cooperative group setting. Eligibility included age  $\geq 18$ , recurrent or progressive GBM after standard chemoradiation. Treatment was intravenous bevacizumab 10 mg/kg and either irinotecan (CPT) 125 mg/m

Journal Title: Journal of neuro-oncology

PUBMED ID: 27695068

DOI: doi.org/10.1371/journal.pone.0164051

Titolo: Enhancing Predicted Efficacy of Tumor Treating Fields Therapy of Glioblastoma Using Targeted Surgical Craniectomy: A Computer Modeling Study.

Autori: Korshoej AR., Saturnino GB., Rasmussen LK., von Oettingen G., Sørensen JC., Thielscher A.

Data di Pubblicazione: 2016-10-4

Abstract: Our results provide theoretical evidence that small and clinically feasible craniectomies may provide significant enhancement of TTF fields intensity in cerebral hemispheric tumors without severely compromising brain protection or causing unacceptable heating in healthy tissues. A clinical trial is being planned to validate safety and efficacy.

Journal Title: PloS one

PUBMED ID: 27690657

DOI: doi.org/10.3171/2016.7.FOCUS16234

Titolo: Laser interstitial thermal therapy for newly diagnosed and recurrent glioblastoma.

Autori: Thomas JG., Rao G., Kew Y., Prabhu SS.

Data di Pubblicazione: 2016-10-4

Abstract: OBJECTIVE Glioblastoma (GBM) is the most common and deadly malignant primary brain tumor. Better surgical therapies are needed for newly diagnosed GBMs that are difficult to resect and for GBMs that recur despite standard therapies. The authors reviewed their institutional experience of using laser interstitial thermal therapy (LITT) for the treatment of newly diagnosed or recurrent GBMs. METHODS This study reports on the pre-LITT characteristics and post-LITT outcomes of 8 patients with newly diagnosed GBMs and 13 patients with recurrent GBM who underwent LITT. RESULTS Compared with the group with recurrent GBMs, the patients with newly diagnosed GBMs who underwent LITT tended to be older (60.8 vs 48.9 years), harbored larger tumors (22.4 vs 14.6 cm

Journal Title: Neurosurgical focus

PUBMED ID: 27690656

DOI: doi.org/10.3171/2016.7.FOCUS16236

Titolo: Stereotactic laser ablation for hypothalamic and deep intraventricular lesions.

Autori: Buckley RT., Wang AC., Miller JW., Novotny EJ., Ojemann JG.

Data di Pubblicazione: 2016-10-4

Abstract: OBJECTIVE Laser ablation is a novel, minimally invasive procedure that utilizes MRI-guided thermal energy to treat epileptogenic and other brain lesions. In addition to treatment of mesial temporal lobe epilepsy, laser



ablation is increasingly being used to target deep or inoperable lesions, including hypothalamic hamartoma (HH), subependymal giant cell astrocytoma (SEGA), and exophytic intrinsic hypothalamic/third ventricular tumors. The authors reviewed their early institutional experience with these patients to characterize clinical outcomes in patients undergoing this procedure. METHODS A retrospective cohort (n = 12) of patients undergoing laser ablation at a single institution was identified, and clinical and radiographic records were reviewed. RESULTS Laser ablation was successfully performed in all patients. No permanent neurological or endocrine complications occurred; 2 (17%) patients developed acute obstructive hydrocephalus or shunt malfunction following treatment. Laser ablation of HH resulted in seizure freedom (Engel Class I) in 67%, with the remaining patients having a clinically significant reduction in seizure frequency of greater than 90% compared with preoperative baseline (Engel Class IIB). Treatment of SEGAs resulted in durable clinical and radiographic tumor control in 2 of 3 cases, with one patient receiving adjuvant everolimus and the other receiving no additional therapy. Palliative ablation of hypothalamic/third ventricular tumors resulted in partial tumor control in 1 of 3 patients. CONCLUSIONS Early experience suggests that laser ablation is a generally safe, durable, and effective treatment for patients harboring HHs. It also appears effective for local control of SEGAs, especially in combination therapy with everolimus. Its use as a palliative treatment for intrinsic hypothalamic/deep intraventricular tumors was less successful and associated with a higher risk of serious complications. Additional experience and long-term follow-up will be beneficial in further characterizing the effectiveness and risk profile of laser ablation in treating these lesions in comparison with conventional resective surgery or stereotactic radiosurgery.

Journal Title: Neurosurgical focus

PUBMED ID: 27686946

DOI: doi.org/10.1016/S1470-2045(16)30313-8

Titolo: Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study.

Autori: Baumert BG., Hegi ME., van den Bent MJ., von Deimling A., Gorlia T., Hoang-Xuan K., Brandes AA., Kantor G., Taphoorn MJB., Hassel MB., Hartmann C., Ryan G., Capper D., Kros JM., Kurscheid S., Wick W., Enting R., Reni M., Thiessen B., Dhermain F., Bromberg JE., Feuvret L., Reijneveld JC., Chinot O., Gijtenbeek JMM., Rossiter JP., Dif N., Balana C., Bravo-Marques J., Clement PM., Marosi C., Tzuk-Shina T., Nordal RA., Rees J., Lacombe D., Mason WP., Stupp R.

Data di Pubblicazione: 2016-10-1

Abstract: Merck Sharpe & Dohme-Merck & Co, Canadian Cancer Society, Swiss Cancer League, UK National Institutes of Health, Australian National Health and Medical Research Council, US National Cancer Institute, European Organisation for Research and Treatment of Cancer Cancer Research Fund.

Journal Title: The Lancet. Oncology

PUBMED ID: 27680966

DOI: doi.org/10.23736/S0390-5616.16.03874-1

Titolo: Second line treatment of recurrent glioblastoma with sunitinib: results of a phase II study and systematic review of literature.

Autori: Grisanti S., Ferrari VD., Buglione M., Agazzi GM., Liserre R., Poliani L., Buttolo L., Gipponi S., Pedersini R., Consoli F., Panciani P., Roca E., Spena G., Triggiani L., Berruti A., Berruti A.

Data di Pubblicazione: 2016-9-30

Abstract: Results of this trial and those of the systematic review indicate that, compared to conventional chemotherapy or bevacizumab, sunitinib has in

sufficient activity in the setting of recurrent GBM. Better patient's molecular stratification for second-line treatment in GBM is warranted.  
Journal Title: Journal of neurosurgical sciences

PUBMED ID: 27662616

DOI: doi.org/10.1016/j.ejca.2016.08.008

Titolo: Prognostic factors of overall survival in children and adolescents enrolled in dose-finding trials in Europe: An Innovative Therapies for Children with Cancer study.

Autori: Carceller F., Bautista FJ., Jiménez I., Hladun-Álvaro R., Giraud C., Bergamaschi L., Dandapani M., Aerts I., Doz F., Frappaz D., Casanova M., Morland B., Hargrave DR., Marshall LV., Vassal G., Pearson AD., Geoerger B., Moreno L.

Data di Pubblicazione: 2016-9-24

Abstract: Performance status of 90-100% and school/work attendance at enrollment are strong indicators of longer OS in paediatric phase I trials. Adult predictive scores correlate with survival in adolescents. These findings provide a useful orientation about potential prognosis and could lead in the future to more paediatric-adapted eligibility criteria in early-phase trials.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 27659836

DOI: doi.org/10.1007/s00381-016-3132-0

Titolo: Conventional chemotherapy and perspectives for molecular-based oncological treatment in pediatric hemispheric low-grade gliomas.

Autori: Fernández MB., Alonso VP.

Data di Pubblicazione: 2016-9-24

Abstract: Recent molecular advances have led to a better understanding of the molecular pathways involved in the biology of LGG, allowing the development of promising tumor-specific, molecularly targeted therapies.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 27659831

DOI: doi.org/10.1007/s00381-016-3148-5

Titolo: Clinical considerations and surgical approaches for low-grade gliomas in deep hemispheric locations: thalamic lesions.

Autori: Wong TT., Chen HH., Liang ML., Hsieh KL., Yang YS., Ho DM., Chang KP., Lee YY., Lin SC., Hsu TR., Chen YW., Yen SH., Chang FC., Guo WY., Chen KW., Kwang WK., Hou WY., Wang CY.

Data di Pubblicazione: 2016-9-24

Abstract: Thalamic LGGs are mainly LGAs and are indolent. The rate of >90 % resection was relatively low in the present series. By applying contemporary diagnostic MRI studies, surgical facilities, and appropriate approaches in selective cases, we may try maximum neuroprotective radical (>90 %) resection.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 27590514

DOI: doi.org/10.18632/oncotarget.11756

Titolo: Radiation combined with temozolomide contraindicated for young adults diagnosed with anaplastic glioma.

Autori: Yang P., Zhang C., Cai J., You G., Wang Y., Qiu X., Li S., Wu C., Yao K., Li W., Peng X., Zhang W., Jiang T.

Data di Pubblicazione: 2016-9-4

Abstract: We observed no survival benefit in young adults (age < 50) with an aplastic glioma when treated with TMZ combined with RT. Our findings warrant further investigation of younger patients diagnosed with anaplastic glioma treated with radiotherapy plus TMZ chemotherapy.  
Journal Title: Oncotarget

PUBMED ID: 27573687

DOI: doi.org/10.1007/s00401-016-1611-8

Titolo: Prognostic impact of the 2016 WHO classification of diffuse gliomas in the French POLA cohort.

Autori: Tabouret E., Nguyen AT., Dehais C., Carpentier C., Ducray F., Idhah A., Mokhtari K., Jouvret A., Uro-Coste E., Colin C., Chinot O., Loiseau H., Moyat E., Maurage CA., Polivka M., Lechapt-Zalcman E., Desenclos C., Meyronet D., Delattre JY., Figarella-Branger D., Figarella-Branger D.

Data di Pubblicazione: 2016-8-31

Abstract: The new WHO classification of diffuse gliomas has been refined and now includes the 1p/19q codeletion, IDH1/2 mutation, and histone H3-K27M mutation. Our objective was to assess the prognostic value of the updated 2016 WHO classification in the French POLA cohort. All cases of high-grade oligodendroglial tumors sent for central pathological review and included into the French nationwide POLA cohort were reclassified according to the updated 4th WHO classification. In total, 1041 patients were included, with a median age at diagnosis of 50.4 years (range 17.1-84.4). Based on the new histomolecular classification, diagnoses included anaplastic oligodendroglioma IDH mutant and 1p/19q-codeleted (32.5 %), anaplastic astrocytoma IDH mutant (IDH (mut)) (11.0 %), anaplastic astrocytoma IDH wild type (IDH (wt)) (5.3 %), glioblastoma IDH (mut) (17.1 %), and glioblastoma IDH (wt) (33.2 %). Ten patients presented with a diffuse midline tumor, H3 K27M mutant. The new WHO classification was prognostic for progression-free survival (PFS) and overall survival (OS) ( $p < 0.001$ ). We did not find prognosis differences between grades III and IV for IDH (mut) 1p/19q intact and IDH (wt) gliomas in univariate and multivariate analyses. Among anaplastic astrocytoma IDH (wt), cases with chromosome arm 7p gain and 10q loss (55 %) had shorter PFS than the others ( $p = 0.027$ ). In conclusion, the new WHO histomolecular classification of diffuse gliomas presented with high prognostic value. Grading was not discriminant between grade III and IV high-grade gliomas.

Journal Title: Acta neuropathologica

PUBMED ID: 27573663

DOI: doi.org/10.1200/JCO.2016.68.1585

Titolo: Phase II Weekly Vinblastine for Chemotherapy-Naïve Children With Progressive Low-Grade Glioma: A Canadian Pediatric Brain Tumor Consortium Study

Autori: Lassaletta A., Scheinemann K., Zelcer SM., Hukin J., Wilson BA., Jabado N., Carret AS., Lafay-Cousin L., Larouche V., Hawkins CE., Pond GR., Poskitt K., Keene D., Johnston DL., Eisenstat DD., Krishnatry R., Mistry M., Arnoldo A., Ramaswamy V., Huang A., Bartels U., Tabori U., Bouffet E.

Data di Pubblicazione: 2016-8-31

Abstract: Purpose Vinblastine monotherapy has shown promising activity and a low-toxicity profile in patients with pediatric low-grade glioma (PLGG) who experienced treatment failure after initial treatment with chemotherapy and/or radiation. The aim of this study was to assess the activity of vinblastine in therapy-naïve children. Patients and Methods Patients < 18 years old with unresectable and/or progressive therapy-naïve PLGG were eligible. Vinblastine was administered once per week at a dose of 6 mg/m<sup>2</sup>.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 27515827

DOI: doi.org/10.1093/neuonc/now091

Titolo: Evaluation of pseudoprogression rates and tumor progression patterns in a phase III trial of bevacizumab plus radiotherapy/temozolomide for newly diagnosed glioblastoma.

Autori: Wick W., Chinot O.L., Bendszus M., Mason W., Henriksson R., Saran F., Nishikawa R., Revil C., Kerloeguen Y., Cloughesy T.

Data di Pubblicazione: 2016-8-13

Abstract: Pseudoprogression complicated progression assessment in a small but relevant number of patients but had negligible impact on PFS. Bevacizumab did not appear to adversely impact tumor progression patterns.

Journal Title: Neuro-oncology

PUBMED ID: 27503138

DOI: doi.org/10.1186/s40478-016-0351-2

Titolo: A combination of TERT promoter mutation and MGMT methylation status predicts clinically relevant subgroups of newly diagnosed glioblastomas.

Autori: Arita H., Yamasaki K., Matsushita Y., Nakamura T., Shimokawa A., Takami H., Tanaka S., Mukasa A., Shirahata M., Shimizu S., Suzuki K., Saito K., Kobayashi K., Higuchi F., Uzuka T., Otani R., Tamura K., Sumita K., Ohno M., Miyakita Y., Kagawa N., Hashimoto N., Hatae R., Yoshimoto K., Shinojima N., Nakamura H., Kanemura Y., Okita Y., Kinoshita M., Ishibashi K., Shofuda T., Kodama Y., Mori K., Tomogane Y., Fukai J., Fujita K., Terakawa Y., Tsuyuguchi N., Moriuchi S., Nonaka M., Suzuki H., Shibuya M., Maehara T., Saito N., Nagane M., Kawahara N., Ueki K., Yoshimine T., Miyaoka E., Nishikawa R., Komori T., Narita Y., Ichimura K.

Data di Pubblicazione: 2016-8-10

Abstract: The prognostic impact of TERT mutations has been controversial in IDH-wild tumors, particularly in glioblastomas (GBM). The controversy may be attributable to presence of potential confounding factors such as MGMT methylation status or patients' treatment. This study aimed to evaluate the impact of TERT status on patient outcome in association with various factors in a large series of adult diffuse gliomas. We analyzed a total of 951 adult diffuse gliomas from two cohorts (Cohort 1, n=758; Cohort 2, n=193) for IDH1/2, 1p/19q, and TERT promoter status. The combined IDH/TERT classification divided Cohort 1 into four molecular groups with distinct outcomes. The overall survival (OS) was the shortest in IDH wild-type/TERT mutated groups, which mostly consisted of GBMs ( $P < 0.0001$ ). To investigate the association between TERT mutations and MGMT methylation on survival of patients with GBM, samples from a combined cohort of 453 IDH-wild-type GBM cases treated with radiation and temozolomide were analyzed. A multivariate Cox regression model revealed that the interaction between TERT and MGMT was significant for OS ( $P = 0.0064$ ). Compared with TERT mutant-MGMT unmethylated GBMs, the hazard ratio (HR) for OS incorporating the interaction was the lowest in the TERT mutant-MGMT methylated GBM (HR, 0.266), followed by the TERT wild-type-MGMT methylated (HR, 0.317) and the TERT wild-type-MGMT unmethylated GBMs (HR, 0.542). Thus, patients with TERT mutant-MGMT unmethylated GBM have the poorest prognosis. Our findings suggest that a combination of IDH, TERT, and MGMT refines the classification of grade II-IV diffuse gliomas.

Journal Title: Acta neuropathologica communications

PUBMED ID: 27502586

DOI: doi.org/10.1186/s12883-016-0658-4

Titolo: EFFECTS: an expanded access program of everolimus for patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex.

Autori: Fogarasi A., De Waele L., Bartalini G., Jozwiak S., Laforgia N., Verhelst H., Petrak B., Pedespan JM., Witt O., Castellana R., Crippa S., Gislimberti G., Gyorsok Z.

Data di Pubblicazione: 2016-8-10

Abstract: This study confirms the acceptable safety profile of everolimus in patients with SEGA associated with TSC in a real-world setting. The results further support the efficacy of everolimus in the treatment of SEGA associated with TSC. (EudraCT: 2010-022583-13).

Journal Title: BMC neurology

PUBMED ID: 27501915

DOI: doi.org/10.1007/s11864-016-0430-4

Titolo: The Role of Molecular Diagnostics in the Management of Patients with Gliomas.

Autori: Wirsching HG., Weller M.

Data di Pubblicazione: 2016-8-10

Abstract: The revised World Health Organization (WHO) classification of tumors of the central nervous system of 2016 combines biology-driven molecular marker diagnostics with classical histological cancer diagnosis. Reclassification of gliomas by molecular similarity beyond histological boundaries improves outcome prediction and will increasingly guide treatment decisions. This change in paradigms implies more personalized and eventually more efficient therapeutic approaches, but the era of molecular targeted therapies for gliomas is yet at its onset. Promising results of molecularly targeted therapies in genetically less complex gliomas with circumscribed growth such as subependymal giant cell astrocytoma or pilocytic astrocytoma support further development of molecularly targeted therapies. In diffuse gliomas, several molecular markers that predict benefit from alkylating agent chemotherapy have been identified in recent years. For example, co-deletion of chromosome arms 1p and 19q predicts benefit from polychemotherapy with procarbazine, CCNU (lomustine), and vincristine (PCV) in patients with anaplastic oligodendroglioma, and the presence of 1p/19q co-deletion was integrated as a defining feature of oligodendroglial tumors in the revised WHO classification. However, the tremendous increase in knowledge of molecular drivers of diffuse gliomas on genomic, epigenetic, and gene expression levels has not yet translated into effective molecular targeted therapies. Multiple reasons account for the failure of early clinical trials of molecularly targeted therapies in diffuse gliomas, including the lack of molecular entry controls as well as pharmacokinetic and pharmacodynamics issues, but the key challenge of specifically targeting the molecular backbone of diffuse gliomas is probably extensive clonal heterogeneity. A more profound understanding of clonal selection, alternative activation of oncogenic signaling pathways, and genomic instability is warranted to identify effective combination treatments and ultimately improve survival.

Journal Title: Current treatment options in oncology

PUBMED ID: 27475318

DOI: doi.org/10.1016/j.jocn.2016.06.014

Titolo: The survival significance of a measurable enhancing lesion after completing standard treatment for newly diagnosed glioblastoma.

Autori: Kim SK., Kim TM., Lee ST., Lee SH., Heo DS., Kim IH., Kim DG., Jung HW., Choi SH., Lee SH., Park CK.

Data di Pubblicazione: 2016-8-1

Abstract: The goal of this study was to analyze the survival outcome according to the treatment response after completing standard treatment protocol for newly diagnosed glioblastoma (GBM) and to suggest a patient who should be considered for further treatment. After approving by our Institutional Review Board, 57 patients (38 male, 19 female; median age, 52years; age range, 16

-81years) with newly diagnosed GBM who completed standard treatment protocol were examined retrospectively. According to the treatment response using the RANO criteria, there were 20 patients with complete response (CR), five patients with partial response (PR), 13 patients with stable disease (SD) and 19 patients with progressive disease (PD) after the completion of standard treatment. Patients (PR+SD+PD) with a measurable enhancing lesion were categorized the MEL group (n=37). We analyzed the difference of survival outcome between CR group and MEL group. The median progression-free survival (PFS) in the CR group was significantly better than that of the MEL group (18.0months vs. 3.0months,  $p=0.004$ ). The median overall survival (OS) was also significantly longer in the CR group (25.0months vs. 15.0months,  $p=0.005$ ). However, there was no significant difference in the survival outcome of the CR group compared with that of the subset of MEL group patients who showed PR or SD. Poor survival outcome was found only in MEL group patients who exhibited progression. Patients with a measurable enhancing lesion showing progression after completion of standard treatment protocol are appropriate candidates for further treatment.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 27473815

DOI: doi.org/10.1016/j.ijrobp.2016.05.009

Titolo: Phase 1 Study of Preoperative Chemoradiation Therapy With Temozolomide and Capecitabine in Patients With Locally Advanced Rectal Cancer.

Autori: Jeong JH., Hong YS., Park Y., Kim J., Kim JE., Kim KP., Kim SY., Park JH., Kim JH., Park IJ., Lim SB., Yu CS., Kim JC., Kim TW.

Data di Pubblicazione: 2016-7-31

Abstract: There was a tendency toward higher pCR rates in patients with hypermethylated MGMT. Future randomized studies are therefore warranted.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 27466078

DOI: doi.org/10.1620/tjem.239.269

Titolo: Expression of ADP-ribosyltransferase 1 Is Associated with Poor Prognosis of Glioma Patients.

Autori: Li Z., Yan X., Sun Y., Yang X.

Data di Pubblicazione: 2016-7-29

Abstract: Glioma has a poor prognosis due to its rapid overgrowth, diffuse invasion, and chemotherapy resistance. The improvements in clinical outcome are still limited and the identification of novel biomarkers involved in the progression of gliomas is still under critical demands. Amino acid ADP-ribosyltransferase 1 (ART1) is an enzyme that catalyzes the mono-ADP-ribosylation, a reversible post-translational modification. For example, the mono-ADP-ribosylation of transcription factors can affect their binding to target gene promoters. However, the functional significance of ART1 in glioma has not been reported. We collected 107 glioma cases from Qianfoshan Hospital and Yidu Central Hospital of Weifang between April 2008 and September 2015 to analyze the prognosis value of ART1 in gliomas. RT-qPCR analysis showed that the expression level of ART1 mRNA in glioma tissues was 4-fold higher than that in normal brain tissues. According to the immunohistochemical staining results, 44 patients (41.1%) were categorized as ART1 positive ( $\geq 20\%$  of stained glioma cells), while the other 63 patients (58.9%) categorized as ART1 negative ( $< 20\%$  of stained glioma cells). Moreover, the mean percentage of ART1-positive cells was 43.7%, 53.6% and 64.2% in WHO grade II, III and IV specimens, respectively. Through univariate and multivariate analyses, we identified ART1 as an independent prognostic factor. We also found that ART1 overexpression in U251 glioblastoma cells could significantly decrease the susceptibility to vincristine, one of tubulin-targeted drugs, which is widely used in cli

nical treatment for glioma. Taken together, we propose that up-regulation of ART1 expression is associated with the aggressiveness of glioma.  
Journal Title: The Tohoku journal of experimental medicine

PUBMED ID: 27461038

DOI: doi.org/10.1007/s11864-016-0422-4

Titolo: Relapsed Glioblastoma: Treatment Strategies for Initial and Subsequent Recurrences.

Autori: Tosoni A., Franceschi E., Poggi R., Brandes AA.

Data di Pubblicazione: 2016-7-28

Abstract: At the time of glioblastoma (GBM) recurrence, a sharp analysis of prognostic factors, disease characteristics, response to adjuvant treatment, and clinical conditions should be performed. A prognostic assessment could allow a careful selection between patients that could be proposed to intensified approaches or palliative setting. Participation in clinical trials aims to improve outcome, and should be encouraged due to dismal prognosis of GBM patients after recurrence. Reoperation should be proposed if the tumor is amenable to a complete resection and if prognostic factors suggest that patient could benefit from a second surgery. Second-line chemotherapy should be chosen based on MGMT status, time to disease recurrence, and toxicity profile. If enrollment into a clinical trial is not possible, a nitrosourea-based regimen is the preferred choice, carefully evaluating any previous temozolomide (TMZ)-related toxicity. In MGMT-methylated patients relapsing after TMZ completion, a rechallenge could be proposed. After second progression, the clinical advantage of subsequent lines of chemotherapy still needs to be clarified. However, based on performance status, patients' preference, and disease behavior, a third-line treatment could be considered. Available treatments include nitrosoureas, bevacizumab, or carboplatin plus etoposide. However, more effective therapeutic options are needed.

Journal Title: Current treatment options in oncology

PUBMED ID: 27423645

DOI: doi.org/10.1007/s11060-016-2202-1

Titolo: Relapse patterns and outcome after relapse in standard risk medulloblastoma: a report from the HIT-SIOP-PNET4 study.

Autori: Sabel M., Fleischhack G., Tippelt S., Gustafsson G., Doz F., Kortmann R., Massimino M., Navajas A., von Hoff K., Rutkowski S., Warmuth-Metz M., Clifford SC., Pietsch T., Pizer B., Lannering B., Lannering B.

Data di Pubblicazione: 2016-7-18

Abstract: The HIT-SIOP-PNET4 randomised trial for standard risk medulloblastoma (MB) (2001-2006) included 338 patients and compared hyperfractionated and conventional radiotherapy. We here report the long-term outcome after a median follow up of 7.8 years, including detailed information on relapse and the treatment of relapse. Data were extracted from the HIT Group Relapsed MB database and by way of a specific case report form. The event-free and overall (OS) survival at 10 years were  $76\pm 2\%$  and  $78\pm 2\%$  respectively with no significant difference between the treatment arms. Seventy-two relapses and three second malignant neoplasms were reported. Thirteen relapses (18%) were isolated local relapses in the posterior fossa (PF) and 59 (82%) were craniospinal, metastatic relapses (isolated or multiple) with or without concurrent PF disease. Isolated PF relapse vs all other relapses occurred at mean/median of 38/35 and 28/26 months respectively ( $p=0.24$ ). Late relapse, i.e.  $>5$  years from diagnosis, occurred in six patients (8%). Relapse treatment consisted of combinations of surgery (25%), focal radiotherapy (RT 22%), high dose chemotherapy with stem cell rescue (HDSCR 21%) and conventional chemotherapy (90%). OS at 5 years after relapse was  $6.0\pm 4\%$ . In multivariate analysis; isolated relapse in PF, and surgery were significantly associated with prolong

ed survival whereas RT and HDSCR were not. Survival after relapse was not related to biological factors and was very poor despite several patients receiving intensive treatments. Exploration of new drugs is warranted, preferably based on tumour biology from biopsy of the relapsed tumour.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 27422128

DOI: doi.org/10.1007/s11060-016-2206-x

Titolo: Impact of tapering and discontinuation of bevacizumab in patients with progressive glioblastoma.

Autori: Hertenstein A., Hielscher T., Menn O., Wiestler B., Winkler F., Platten M., Wick W., Wick A.

Data di Pubblicazione: 2016-7-17

Abstract: Bevacizumab is frequently used in patients with progressive glioblastoma raising questions regarding frequency of treatments, dosage, duration of therapy and the possibility of tapering and discontinuation for selected patient groups. We retrospectively assessed the safety and outcome of tapering and discontinuation of bevacizumab therapy for reasons other than disease progression and toxicity in 19 patients with progressive glioblastoma receiving bevacizumab for at least 6 months. In 10 of the 19 patients tapering bevacizumab resulted in complete discontinuation and reinitiation after disease progression during halted treatment. As a comparison group 33 patients with bevacizumab for at least 6 months continuously dosed at 10 mg/kg every 2 weeks were selected. Age and Karnofsky performance status at start of bevacizumab were similar in both groups. Influenced by the selection process, progression-free survival (PFS) and overall survival (OS) were longer in the group receiving a tapered and discontinued bevacizumab regimen (PFS 22.7 versus 11.2 months, HR 0.33, p-value=0.01; OS 29.9 versus 15.5 months, HR 0.22, p-value=0.001) with a median time of discontinuation of 4.5 months (range: 1.9-44.2 months). Stable disease or partial response according to RANO at ≥3 months was achieved in 89% of patients with reinitiated bevacizumab therapy after discontinuation. These data indicate that tapering and discontinuation of bevacizumab therapy for other reasons than progression is feasible without an increased risk for tumor rebound or unresponsiveness to reinitiated bevacizumab therapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 27411023

DOI: doi.org/10.1080/14712598.2016.1212012

Titolo: Recent advances and future of immunotherapy for glioblastoma.

Autori: Kamran N., Calinescu A., Candolfi M., Chandran M., Mineharu Y., Asad AS., Koschmann C., Nunez FJ., Lowenstein PR., Castro MG.

Data di Pubblicazione: 2016-7-14

Abstract: Encouraging results have been observed with immunotherapeutic strategies; some clinical trials are reaching phase III. Significant progress has been made in unraveling the molecular and genetic heterogeneity of GBM and its implications to disease prognosis. There is now consensus related to the critical need to incorporate tumor heterogeneity into the design of therapeutic approaches. Recent data also indicates that an efficacious treatment strategy will need to be combinatorial and personalized to the tumor genetic signature.

Journal Title: Expert opinion on biological therapy

PUBMED ID: 27393350

DOI: doi.org/10.1007/s11060-016-2188-8



Titolo: The effects of sequential treatments on hippocampal volumes in malignant glioma patients.

Autori: Nolen SC., Lee B., Shantharam S., Yu HJ., Su L., Billimek J., Bota D A.

Data di Pubblicazione: 2016-7-10

Abstract: Malignant gliomas (MG) are very aggressive tumors. In an effort to improve the outcome, the patients receive multi-modal therapies such as surgery, radiation and chemotherapy (temozolomide followed in many cases by bevacizumab). The survivors are affected by multiple learning and memory deficits. Greater deterioration over time in hippocampal specific cognitive tasks was shown in patients receiving bevacizumab in addition to radiation and temozolomide for a longer period of time (RTOG 0825). The rate of hippocampal atrophy in patients treated with radiation and temozolomide followed by bevacizumab is not yet determined, and is the goal of the present study. We used the serial MRIs obtained as parts of standard clinical care in patients with MG. Measurements were done using the Medical Image Processing, Analysis and Visualization (MIPAV) software. The hippocampus in the contralateral hemisphere was manually traced and measured, to avoid morphological structure changes induced by the tumor, radiation fields or surgical markers. We determined a longitudinal progression of hippocampal atrophy-with the maximum volume loss (33.26%) for the patients that were on treatment for 5 years. There was no detectable hippocampal atrophy during the chemo-radiation followed by adjuvant temozolomide. A significant decrease in the absolute hippocampus volume was noted after 6 months of continuous bevacizumab treatment ( $p < 0.05$ ). The hippocampal volume loss progressed over the next 3 years, and was higher than the one previously reported in Alzheimer disease patients. The hippocampal volume loss is minimal during the 1 month after diagnosis, when the patients receive chemo-radiation and adjuvant temozolomide. However, prolonged treatment including bevacizumab is associated with a significant rate of hippocampal volume loss.

Journal Title: Journal of neuro-oncology

PUBMED ID: 27378212

DOI: doi.org/10.1002/14651858.CD010439.pub2

Titolo: Radiotherapy for diffuse brainstem glioma in children and young adults.

Autori: Hu X., Fang Y., Hui X., Jv Y., You C.

Data di Pubblicazione: 2016-7-6

Abstract: We could make no definitive conclusions from this review based on the currently available evidence. Further research is needed to establish the role of radiotherapy in the management of newly diagnosed diffuse brainstem glioma in children and young adults. Future RCTs should be conducted with adequate power and all relevant outcomes should be taken into consideration. Moreover, international multicentre collaboration is encouraged. Considering the potential advantage of hypofractionated radiotherapy to decrease the treatment burden and increase the quality of remaining life, we suggest that more attention should be paid to hypofractionated radiotherapy.

Journal Title: The Cochrane database of systematic reviews

PUBMED ID: 27377654

DOI: doi.org/10.1007/s11060-016-2190-1

Titolo: Pembrolizumab: first experience with recurrent primary central nervous system (CNS) tumors.

Autori: Blumenthal DT., Yalon M., Vainer GW., Lossos A., Yust S., Tzach L., Cagnano E., Limon D., Bokstein F.

Data di Pubblicazione: 2016-7-6

**Abstract:** Patients with progressive primary brain tumors (PBT) are attracted to promising new treatments, even prior to convincing data. Anti-PD1 immunotherapies have been in the spotlight since publication of groundbreaking results for metastatic melanoma with pembrolizumab (PBL). Our objective was to report on the response and toxicity of PBL in patients with advanced PBT. We retrospectively reviewed the charts of 22 patients (17 adults and 5 children) with recurrent central nervous system tumors treated with PBL. We analyzed prior antineoplastic therapies, steroid usage, and outcomes. Patients received a median of two neoplastic therapies prior to PBL, and a median of three infusions of PBL in adults and four in children. Twelve patients (9 adults and 3 children) started PBL on steroids (median dose in adults 4 mg; range 2-8, and in children 1.5 mg, range 0.5-4) and five patients received steroids later during PBL treatment. Twelve patients (10 adults and 2 children) received concomitant bevacizumab with PBL. Side effects were minimal. All patients showed progressive tumor growth during therapy. Median OS from the start of PBL was 2.6 months in adults and 3.2 months in children. Two GB patients underwent tumor resection following treatment with PBL. Tumor-lymphocytic response in these cases was unremarkable, and PD-L1 immuno-staining was negative. In this series of 22 patients with recurrent primary brain tumors, PBL showed no clinical or histologic efficacy. We do not recommend further use of PBL for recurrent PBT unless convincing prospective clinical trial data are published.

Journal Title: Journal of neuro-oncology

PUBMED ID: 27375228

DOI: doi.org/10.1016/j.critrevonc.2016.05.012

Titolo: Childhood medulloblastoma.

Autori: Massimino M., Biassoni V., Gandola L., Garre ML., Gatta G., Giangaspero F., Poggi G., Rutkowski S.

Data di Pubblicazione: 2016-7-5

**Abstract:** Medulloblastoma accounts for 15-20% of childhood nervous system tumors. The risk of dying was reduced by 30% in the last twenty years. Patients are divided in risk strata according to post-surgical disease, dissemination, histology and some molecular features such as WNT subgroup and MYC status. Sixty to 70% of patients older than 3 years are assigned to the average-risk group. High-risk patients include those with disseminated and/or residual disease, large cell and/or anaplastic histotypes, MYC genes amplification. Current and currently planned clinical trials will: (1) evaluate the feasibility of reducing both the dose of craniospinal irradiation and the volume of the posterior fossa radiotherapy (RT) for those patients at low biologic risk, commonly identified as those having a medulloblastoma of the WNT subgroup; (2) determine whether intensification of chemotherapy (CT) or irradiation can improve outcome in patients with high-risk disease; (3) find target therapies allowing tailored therapies especially for relapsing patients and those with higher biological risk.

Journal Title: Critical reviews in oncology/hematology

PUBMED ID: 27371575

DOI: doi.org/10.1158/2159-8290.CD-16-0563

Titolo: CDK4/6 Inhibitors: Promising Opportunities beyond Breast Cancer.

Autori: Lim JS., Turner NC., Yap TA.

Data di Pubblicazione: 2016-7-3

**Abstract:** Patnaik and colleagues report on the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of abemaciclib for the treatment of advanced solid cancers, demonstrating antitumor activity in advanced breast cancers as well as glioblastoma, melanoma, non-small cell lung cancer, colorectal cancer, and ovarian cancer. The development of abemaciclib and other CDK4/6 inhibitors should now be fully optimized through the use of novel pred

ictive biomarkers of response and rational combinations. Cancer Discov; 6(7); 697-9. ©2016 AACRSee related article by Patnaik et al., p. 740.  
Journal Title: Cancer discovery

PUBMED ID: 27353036

DOI: doi.org/10.1530/ERC-16-0117

Titolo: MGMT expression predicts response to temozolomide in pancreatic neuroendocrine tumors.

Autori: Cros J., Hentic O., Rebours V., Zappa M., Gille N., Theou-Anton N., Vernerey D., Maire F., Lévy P., Bedossa P., Paradis V., Hammel P., Ruszniewski P., Couvelard A.

Data di Pubblicazione: 2016-6-30

Abstract: Temozolomide (TEM) showed encouraging results in well-differentiated pancreatic neuroendocrine tumors (WDPNETs). Low O(6)-methylguanine-DNA methyltransferase (MGMT) expression and MGMT promoter methylation within tumors correlate with a better outcome under TEM-based chemotherapy in glioblastoma. We aimed to assess whether MGMT expression and MGMT promoter methylation could help predict the efficacy of TEM-based chemotherapy in patients with WDPNET. Consecutive patients with progressive WDPNET and/or liver involvement over 50% who received TEM between 2006 and 2012 were retrospectively studied. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines. Nuclear expression of MGMT was assessed by immunohistochemistry (H-score, 0-300) and MGMT promoter methylation by pyrosequencing. Forty-three patients (21 men, 58 years (27-84)) with grade 1 WDPNET (n=6) or 2 (n=36) were analyzed. Objective response, stable disease, and progression rates were seen in 17 patients (39.5%), 18 patients (41.9%), and 8 patients (18.6%), respectively. Low MGMT expression ( $\leq 50$ ) was associated with radiological objective response ( $P=0.04$ ) and better progression-free survival (PFS) (HR=0.35 (0.15-0.81),  $P=0.01$ ). Disease control rate at 18 months of treatment remained satisfying with an MGMT score up to 100 (74%) but dropped with a higher expression. High MGMT promoter methylation was associated with a low MGMT expression and longer PFS (HR=0.37 (0.29-1.08),  $P=0.05$ ). Low MGMT score ( $\leq 50$ ) appears to predict an objective tumor response, whereas an intermediate MGMT score (50-100) seems to be associated with prolonged stable disease.

Journal Title: Endocrine-related cancer

PUBMED ID: 27350411

DOI: doi.org/10.1007/s11060-016-2189-7

Titolo: A molecular biology and phase II study of imetelstat (GRN163L) in children with recurrent or refractory central nervous system malignancies: a pediatric brain tumor consortium study.

Autori: Salloum R., Hummel TR., Kumar SS., Dorris K., Li S., Lin T., Daryani VM., Stewart CF., Miles L., Poussaint TY., Stevenson C., Goldman S., Dhall G., Packer R., Fisher P., Pollack IF., Fouladi M., Boyett J., Drissi R.

Data di Pubblicazione: 2016-6-29

Abstract: Telomerase activation is critical in many cancers including central nervous system (CNS) tumors. Imetelstat is an oligonucleotide that binds to the template region of the RNA component of telomerase, inhibiting its enzymatic activity. We conducted an investigator-sponsored molecular biology (MB) and phase II study to estimate inhibition of tumor telomerase activity and sustained responses by imetelstat in children with recurrent CNS malignancies. In the MB study, patients with recurrent medulloblastoma, high-grade glioma (HGG) or ependymoma undergoing resection received one dose of imetelstat as a 2-h intravenous infusion at 285 mg/m<sup>2</sup>, 12-24 h before surgery. Telomerase activity was evaluated in fresh tumor from surgery. Post-surgery and in the phase II study, patients received imetelstat IV (days 1 and 8 q21-days) at 285 mg/m<sup>2</sup>. Imetelstat pharmacokinetic and pharmacodynamic studies we

re performed. Of two evaluable patients on the MB trial, intratumoral telomerase activity was inhibited by 95% compared to baseline archival tissue in one patient and was inevaluable in one patient. Forty-two patients (40 evaluable for toxicity) were enrolled: 9 medulloblastomas, 18 HGG, 4 ependymomas, 9 diffuse intrinsic pontine gliomas. Most common grade 3/4 toxicities included thrombocytopenia (32.5%), lymphopenia (17.5%), neutropenia (12.5%), ALT (7.5%) and AST (5%) elevation. Two patients died of intratumoral hemorrhage secondary to thrombocytopenia leading to premature study closure. No objective responses were observed. Telomerase inhibition was observed in peripheral blood mononuclear cells (PBMCs) for at least 8 days. Imetelstat demonstrated intratumoral and PBMC target inhibition; the regimen proved too toxic in children with recurrent CNS tumors.

Journal Title: Journal of neuro-oncology

PUBMED ID: 27334978

DOI: doi.org/10.1007/s11864-016-0418-0

Titolo: Targeted Therapeutics in Patients With High-Grade Gliomas: Past, Present, and Future.

Autori: Chen R., Cohen AL., Colman H.

Data di Pubblicazione: 2016-6-24

Abstract: High-grade gliomas remain incurable despite current therapies, which are plagued by high morbidity and mortality. Molecular categorization of glioma subtypes using mutations in isocitrate dehydrogenase 1/2 (IDH1/2), TP53, and ATRX; codeletion of chromosomes 1p and 19q; DNA methylation; and amplification of genes such as epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor, alpha polypeptide provides a more accurate prognostication and biologic classification than classical histopathological diagnoses, and a number of molecular markers are being incorporated in the new World Health Organization classification of gliomas. However, despite the improved understanding of the molecular subtypes of gliomas and the underlying alterations in specific signaling pathways, these observations have so far failed to result in the successful application of targeted therapies, as has occurred in other solid tumors. To date, the only targeted therapy for gliomas approved by the US Food and Drug Administration is bevacizumab, which targets vascular endothelial growth factor. EGFR remains a dominant molecular alteration in specific glioma subtypes and represents a potentially promising target, with drugs of multiple types targeting EGFR in development including vaccines, antibody drug conjugates, and chimeric antigen receptor (CAR) T cells, despite the prior failures of EGFR tyrosine kinase inhibitors. Immune therapies under investigation include checkpoint inhibitors, vaccines against tumor-associated antigens and tumor-specific antigens, pulsed dendritic cells, heat shock protein-tumor conjugates, and CAR T cells. Mutations in the IDH1/2 genes are central to gliomagenesis in a high proportion of grade II and III gliomas, and ongoing trials are examining vaccines against IDH1, small molecular inhibitors of IDH1 and IDH2, and metabolic components including NAD<sup>+</sup> depletion to target IDH-mutated gliomas. The central role of DNA methylation in a subset of gliomas may be targetable, but better understanding of the relation between epigenetic alterations and resulting tumor biology appears necessary. Ultimately, given the prior failure of single-agent targeted therapy in high-grade gliomas, it appears that novel combinatorial therapy or targeted drugs with immunomodulatory or epigenetic approaches will likely be necessary to successfully combat these challenging tumors.

Journal Title: Current treatment options in oncology

PUBMED ID: 27318492

DOI: doi.org/10.1007/s00432-016-2187-3

Titolo: The earlier the better? Bevacizumab in the treatment of recurrent MG MT-non-methylated glioblastoma.

Autori: Schaub C., Schäfer N., Mack F., Stuplich M., Kebir S., Niessen M., Tzaridis T., Banat M., Vatter H., Waha A., Herrlinger U., Glas M.

Data di Pubblicazione: 2016-6-20

Abstract: Our findings suggest that early treatment with BEV in patients with MGMT-non-methylated relapsed GBM is associated with a better PFS, but not with superior OS, possibly implicating that the early, i.e., second-line, use of BEV is not mandatory and BEV treatment may safely be delayed to third-line therapy in this subgroup of patients.

Journal Title: Journal of cancer research and clinical oncology

PUBMED ID: 27311324

DOI: doi.org/10.1186/s40478-016-0331-6

Titolo: ATRX immunostaining predicts IDH and H3F3A status in gliomas.

Autori: Ebrahimi A., Skardelly M., Bonzheim I., Ott I., Mühleisen H., Eckert F., Tabatabai G., Schittenhelm J.

Data di Pubblicazione: 2016-6-18

Abstract: Gliomas are the most frequent intraaxial CNS neoplasms with a heterogeneous molecular background. Recent studies on diffuse gliomas have shown frequent alterations in the genes involved in chromatin remodelling pathways such as  $\alpha$ -thalassemia/mental-retardation-syndrome-X-linked gene (ATRX). Yet, the reliability of ATRX in predicting isocitrate dehydrogenase (IDH) and H3 histone, family 3A (H3F3A) mutations in gliomas, is unclear. We analysed the ATRX expression status by immunohistochemistry, in a large series of 1064 gliomas and analysed the results in correlation to IDH, H3F3A and loss of heterozygosity (LOH) 1p/19q status in these tumors. We also investigated the prognostic potential of ATRX concerning the clinical outcome of patients with diffuse gliomas. According to our results, loss of nuclear ATRX expression was accompanied with an astrocytic tumor lineage and a younger age of onset. ATRX loss in astrocytomas was also strongly associated with IDH1/2 and H3F3A mutation ( $p < 0.0001$ ). Among 196 glial tumors with nuclear ATRX loss, 173 (89 %) had an IDH1 or IDH2 mutation. Among the remaining 23 cases (11 %) with ATRX loss and IDH wild type status, 7 cases had a H3F3A G34R mutation (3 %) and 2 cases had a H3F3A K27M mutation (1 %). ATRX retention in IDH1/2 mutant tumors was strongly associated with LOH 1p/19q and oligodendroglioma histology ( $p < 0.0001$ ). We also confirmed the significant prognostic role of ATRX. Diffuse gliomas with ATRX loss ( $n = 137$ , median 1413 days, 95 % CI: 1065-1860 days) revealed a significantly better clinical outcome compared with tumors with ATRX retention ( $n = 335$ , median: 609, 95 % CI: 539-760 days, HR=1.81,  $p < 0.0001$ ). In conclusion, ATRX is a potential marker for prediction of IDH/H3F3A mutations and substratification of diffuse gliomas into survival relevant tumor groups. Such classification is of great importance for further clinical decision making especially concerning the therapeutic options available for diffuse gliomas.

Journal Title: Acta neuropathologica communications

PUBMED ID: 27306443

DOI: doi.org/10.1007/s11060-016-2167-0

Titolo: Myxopapillary ependymoma: a SEER analysis of epidemiology and outcomes.

Autori: Bates JE., Choi G., Milano MT.

Data di Pubblicazione: 2016-6-17

Abstract: Myxopapillary ependymoma (MPE) is an exceedingly rare tumor histology. While surgery is clearly the treatment of choice, controversy exists regarding the role of adjuvant radiotherapy (RT). Using the Surveillance, epidemiology, and end results (SEER) database, we aimed to determine the epidemi

ology, prognostic factors, and treatment-related outcomes for MPE. A total of 773 cases were found in the SEER database. The incidence in the American population was found to be 1.00 per million person-years. On multivariate analysis, receipt of surgery (HR=0.14, CI=0.06-0.35,  $p<0.001$ ), receipt of RT (HR=4.06, CI=1.87-8.81,  $p<0.001$ ), age less than 30 (HR=0.24, CI=0.08-0.72,  $p=0.01$ ), and Caucasian race (HR=0.37, CI=0.13-0.996,  $p=0.049$ ) were statistically significant prognostic factors. The mean tumor size among those receiving RT (4.6 cm) was significantly larger than among those not receiving RT (3.2 cm,  $p=0.0002$ ). Those who lived in metropolitan areas were more likely to receive RT than those who did not. Given multiple previous studies show that RT improves PFS and the discrepancy in tumor size, selection bias is likely a significant contributor to the apparent negative impact of RT on OS. Regardless, surgery remains the most crucial aspect in the care of patients with MPE.

Journal Title: Journal of neuro-oncology

PUBMED ID: 27287048

DOI: doi.org/10.1186/s12885-016-2399-6

Titolo: Can advanced new radiation therapy technologies improve outcome of high grade glioma (HGG) patients? analysis of 3D-conformal radiotherapy (3DCRT) versus volumetric-modulated arc therapy (VMAT) in patients treated with surgery, concomitant and adjuvant chemo-radiotherapy.

Autori: Navarra P., Pessina F., Cozzi L., Ascolese AM., Lobefalo F., Stravato A., D'Agostino G., Franzese C., Caroli M., Bello L., Scorsetti M.

Data di Pubblicazione: 2016-6-12

Abstract: VMAT resulted superior to 3DCRT in terms of dosimetric findings and clinical results.

Journal Title: BMC cancer

PUBMED ID: 27285546

DOI: doi.org/10.3171/2016.4.JNS152771

Titolo: Eosinophilic meningitis triggered by implanted Gliadel wafers: case report.

Autori: Saito K., Yamasaki K., Yokogami K., Ivanova A., Takeishi G., Sato Y., Takeshima H.

Data di Pubblicazione: 2016-6-11

Abstract: Although carmustine (Gliadel) wafers improve local tumor control and extend the overall survival in patients with malignant glioma, adverse effects have been documented. The authors report the first case of eosinophilic meningitis triggered by the placement of Gliadel wafers. A 61-year-old man with a history of alimentary allergy and glioblastoma in the right frontal lobe underwent resection followed by the implantation of Gliadel wafers. Three weeks later he suffered the sudden onset of headache, vomiting, and progressive consciousness disturbance. Computed tomography revealed enlargement of the ventricular system and subdural space on the side of the tumor. His CSF leukocyte count increased up to 3990 cells/mm

Journal Title: Journal of neurosurgery

PUBMED ID: 27269943

DOI: doi.org/10.1200/JCO.2015.65.7825

Titolo: Therapeutic Impact of Cytoreductive Surgery and Irradiation of Posterior Fossa Ependymoma in the Molecular Era: A Retrospective Multicohort Analysis.

Autori: Ramaswamy V., Hielscher T., Mack SC., Lassaletta A., Lin T., Pajtler KW., Jones DT., Luu B., Cavalli FM., Aldape K., Remke M., Mynarek M., Rutkowski S., Gururangan S., McLendon RE., Lipp ES., Dunham C., Hukin J., Eisensta

t DD., Fulton D., van Landeghem FK., Santi M., van Veelen ML., Van Meir EG., Osuka S., Fan X., Muraszko KM., Tirapelli DP., Oba-Shinjo SM., Marie SK., Carlotti CG., Lee JY., Rao AA., Giannini C., Faria CC., Nunes S., Mora J., Hamilton RL., Hauser P., Jabado N., Petrecca K., Jung S., Massimi L., Zollo M., Cinalli G., Bognár L., Klekner A., Hortobágyi T., Leary S., Ermoian RP., Olson JM., Leonard JR., Gardner C., Grajkowska WA., Chambless LB., Cain J., Eberhart CG., Ahsan S., Massimino M., Giangaspero F., Buttarelli FR., Packer RJ., Emery L., Yong WH., Soto H., Liau LM., Everson R., Grossbach A., Shalaby T., Grotzer M., Karajannis MA., Zagzag D., Wheeler H., von Hoff K., Alonso M., Tuñón T., Schüller U., Zitterbart K., Sterba J., Chan JA., Guzman M., Elbabaa SK., Colman H., Dhall G., Fisher PG., Fouladi M., Gajjar A., Goldman S., Hwang E., Kool M., Ladha H., Vera-Bolanos E., Wani K., Lieberman F., Mikkelsen T., Omuro AM., Pollack IF., Prados M., Robins HI., Soffiatti R., Wu J., Metellus P., Tabori U., Bartels U., Bouffet E., Hawkins CE., Rutka JT., Dirks P., Pfister SM., Merchant TE., Gilbert MR., Armstrong TS., Korshunov A., Ellison DW., Taylor MD.

Data di Pubblicazione: 2016-6-9

Abstract: The most impactful biomarker for posterior fossa ependymoma is molecular subgroup affiliation, independent of other demographic or treatment variables. However, both EPN\_PFA and EPN\_PFB still benefit from increased extent of resection, with the survival rates being particularly poor for subtotally resected EPN\_PFA, even with adjuvant radiation therapy. Patients with EPN\_PFB who undergo gross total resection are at lower risk for relapse and should be considered for inclusion in a randomized clinical trial of observation alone with radiation reserved for those who experience recurrence.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 27253224

DOI: doi.org/10.1371/journal.pone.0155315

Titolo: Addition of Anti-Angiogenetic Therapy with Bevacizumab to Chemo- and Radiotherapy for Leptomeningeal Metastases in Primary Brain Tumors.

Autori: Burger MC., Zeiner PS., Jahnke K., Wagner M., Mittelbronn M., Steinbach JP.

Data di Pubblicazione: 2016-6-3

Abstract: Leptomeningeal dissemination of a primary brain tumor is a condition which is challenging to treat, as it often occurs in rather late disease stages in highly pretreated patients. Its prognosis is dismal and there is still no accepted standard of care. We report here a good clinical effect with a partial response in three out of nine patients and a stable disease with improvement on symptoms in two more patients following systemic anti-angiogenic treatment with bevacizumab (BEV) alone or in combination with chemo- and/or radiotherapy in a series of patients with leptomeningeal dissemination from primary brain tumors (diffuse astrocytoma WHO°II, anaplastic astrocytoma WHO°III, anaplastic oligodendroglioma WHO°III, primitive neuroectodermal tumor and glioblastoma, both WHO°IV). This translated into effective symptom control in five out of nine patients, but only moderate progression-free and overall survival times were reached. Partial responses as assessed by RANO criteria were observed in three patients (each one with anaplastic oligodendroglioma, primitive neuroectodermal tumor and glioblastoma). In these patients progression-free survival (PFS) intervals of 17, 10 and 20 weeks were achieved. In three patients (each one with diffuse astrocytoma, anaplastic astrocytoma and primitive neuroectodermal tumor) stable disease was observed with PFS of 13, 30 and 8 weeks. Another three patients (all with glioblastoma) were primary non-responders and deteriorated rapidly with PFS of 3 to 4 weeks. No severe adverse events were seen. These experiences suggest that the combination of BEV with more conventional therapy schemes with chemo- and/or radiotherapy may be a palliative treatment option for patients with leptomeningeal dissemination of brain tumors.

Journal Title: PloS one

PUBMED ID: 27252150

DOI: doi.org/10.1002/cam4.734

Titolo: Prognostic value of health-related quality of life for death risk stratification in patients with unresectable glioblastoma.

Autori: Paquette B., Vernerey D., Chauffert B., Dabakuyo S., Feuvret L., Taillandier L., Frappaz D., Taillia H., Schott R., Ducray F., Fabbro M., Tennevet I., Ghiringhelli F., Guillamo JS., Durando X., Castera D., Frenay M., Campello C., Dalban C., Skrzypski J., Chinot O., Anota A., Bonnetain F.

Data di Pubblicazione: 2016-6-3

Abstract: Glioblastoma is the most common malignant brain tumor in adults. Baseline health-related quality of life (HRQoL) is a major subject of concern for these patients. We aimed to assess the independent prognostic value of HRQoL in unresectable glioblastoma (UGB) patients for death risk stratification. One hundred and thirty-four patients with UGB were enrolled from the TEMAVIR trial. HRQoL was evaluated at baseline using the EORTC QLQ-C30 and BN20 brain cancer module. Clinical and HRQoL parameters were evaluated in univariable and multivariable Cox analysis as prognostic factors for overall survival (OS). Performance assessment and internal validation of the final model were evaluated with Harrel's C-index, calibration plot, and bootstrap sample procedure. Two OS independent predictors were identified: future uncertainty and sensitivity deficit. The final model exhibited good calibration and acceptable discrimination (C statistic = 0.63). The internal validity of the model was verified with robust uncertainties around the hazard ratio. The prognostic score identified three groups of patients with distinctly different risk profiles with median OS estimated at 16.2, 9.2, and 4.5 months. We demonstrated the additional prognostic value of HRQoL in UGB for death risk stratification and provided a score that may help to guide clinical management and stratification in future clinical trials.

Journal Title: Cancer medicine

PUBMED ID: 27245820

DOI: doi.org/10.1007/s00066-016-0987-7

Titolo: Clinically significant CMV (re)activation during or after radiotherapy/chemotherapy of the brain : Correlation with neurological deterioration and improvement upon antiviral treatment.

Autori: Goerig N., Semrau S., Frey B., Korn K., Fleckenstein B., Überla K., Dörfler A., Putz F., Gaipf US., Fietkau R.

Data di Pubblicazione: 2016-6-2

Abstract: Further prospective studies verifying and investigating this observation in terms of frequency and clinical relevance seem indicated.

Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 27232884

DOI: doi.org/10.1371/journal.pone.0156369

Titolo: Multi-Center Randomized Phase II Study Comparing Cediranib plus Gefitinib with Cediranib plus Placebo in Subjects with Recurrent/Progressive Glioblastoma.

Autori: Brown N., McBain C., Nash S., Hopkins K., Sanghera P., Saran F., Phillips M., Dungey F., Clifton-Hadley L., Wanek K., Krell D., Jeffries S., Khan I., Smith P., Mulholland P.

Data di Pubblicazione: 2016-5-28

Abstract: ClinicalTrials.gov NCT01310855.

Journal Title: PloS one



PUBMED ID: 27194148

DOI: doi.org/10.1093/neuonc/now108

Titolo: Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma.

Autori: Massimino M., Miceli R., Giangaspero F., Boschetti L., Modena P., Antonelli M., Ferroli P., Bertin D., Pecori E., Valentini L., Biassoni V., Garè ML., Schiavello E., Sardi I., Cama A., Viscardi E., Scarzello G., Scoccianti S., Mascarin M., Quaglietta L., Cinalli G., Diletto B., Genitori L., Peretta P., Mussano A., Buccoliero A., Calareso G., Barra S., Mastronuzzi A., Giussani C., Marras CE., Balter R., Bertolini P., Giombelli E., La Spina M., Buttarelli FR., Pollo B., Gandola L.

Data di Pubblicazione: 2016-5-20

Abstract: In a multicenter collaboration, this trial accrued the highest number of patients published so far, and results are comparable to the best single-institution series. The RT boost, when feasible, seemed effective in improving prognosis. Even after multiple procedures, complete resection confirmed its prognostic strength, along with tumor grade. Biological parameters emerging in this series will be the object of future correlatives and reports.  
Journal Title: Neuro-oncology

PUBMED ID: 27193554

DOI: doi.org/10.1007/s11060-016-2144-7

Titolo: Prognostic factors in recurrent glioblastoma patients treated with bevacizumab.

Autori: Schaub C., Tichy J., Schäfer N., Franz K., Mack F., Mittelbronn M., Kebir S., Thiebold AL., Waha A., Filmann N., Banat M., Fimmers R., Steinbach JP., Herrlinger U., Rieger J., Glas M., Bähr O.

Data di Pubblicazione: 2016-5-20

Abstract: The value of bevacizumab (BEV) in recurrent glioblastoma is unclear. Imaging parameters and progression-free survival (PFS) are problematic endpoints. Few data exist on clinical factors influencing overall survival (OS) in unselected patients with recurrent glioblastoma exposed to BEV. We retrospectively analyzed 174 patients with recurrent glioblastoma treated with BEV at two German brain tumor centers. We evaluated general patient characteristics, MGMT status, pretreatment, concomitant oncologic treatment and overall survival. Karnofsky performance score, number of prior chemotherapies, number of prior recurrences and combined treatment with irinotecan (IRI) were significantly associated with OS in univariate analysis. We did not find differences in OS related to sex, age, histology, MGMT status, prior surgical treatment or number of prior radiotherapies. Combined treatment with IRI and higher KPS both remained significantly associated with prolonged survival in multivariate analysis, but patients receiving IRI co-treatment had less advanced disease. Grouping into clinically relevant categories revealed an OS of 16.9 months from start of BEV in patients with first recurrence and KPS  $\geq 80\%$  (n = 25). In contrast, in patients with second recurrence and KPS  $< 80\%$ , OS was 3.6 months (n = 27). Our observational data support an early use of BEV in patients with good performance status. The benefit of co-treatment with IRI in our cohort seems to be the result of biased patient recruitment.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 27189273

DOI: doi.org/10.3349/ymj.2016.57.4.824

Titolo: Re-Irradiation for Recurrent Gliomas: Treatment Outcomes and Prognostic Factors.

Autori: Lee J., Cho J., Chang JH., Suh CO.

Data di Pubblicazione: 2016-5-19

Abstract: Re-irradiation in conjunction with surgery could be a salvage treatment for selected recurrent glioma patients with good performance status and recurrence over a long time.

Journal Title: Yonsei medical journal

PUBMED ID: 27180150

DOI: doi.org/10.1186/s13052-016-0260-9

Titolo: Congenital Glioblastoma multiforme and eruptive disseminated Spitz nevus.

Autori: Mandel VD., Persechini F., Berardi A., Ponti G., Ciardo S., Rossi C., Pellacani G., Farnetani F.

Data di Pubblicazione: 2016-5-16

Abstract: We recommend a close follow-up of these patients with clinical observation, dermoscopy and reflectance confocal microscopy (RCM). However, we suggest a surgical excision of the lesions suspected of being malignant.

Journal Title: Italian journal of pediatrics

PUBMED ID: 27180091

DOI: doi.org/10.1007/s11060-016-2151-8

Titolo: Pseudoprogression in children, adolescents and young adults with non-brainstem high grade glioma and diffuse intrinsic pontine glioma.

Autori: Carceller F., Fowkes LA., Khabra K., Moreno L., Saran F., Burford A., Mackay A., Jones DT., Hovestadt V., Marshall LV., Vaidya S., Mandeville H., Jerome N., Bridges LR., Laxton R., Al-Sarraj S., Pfister SM., Leach MO., Pearson AD., Jones C., Koh DM., Zacharoulis S.

Data di Pubblicazione: 2016-5-16

Abstract: Pseudoprogression (PsP) is a treatment-related phenomenon which hinders response interpretation. Its prevalence and clinical impact have not been evaluated in children/adolescents. We assessed the characteristics, risk factors and prognosis of PsP in children/adolescents and young-adults diagnosed with non-brainstem high grade gliomas (HGG) and diffuse intrinsic pontine gliomas (DIPG). Patients aged 1-21 years diagnosed with HGG or DIPG between 1995 and 2012 who had completed radiotherapy were eligible. PsP was assessed according to study-specific criteria and correlated with first-line treatment, molecular biomarkers and survival. Ninety-one patients (47 HGG, 44 DIPG) were evaluable. Median age: 10 years (range, 2-20). Eleven episodes of PsP were observed in 10 patients (4 HGG, 6 DIPG). Rates of PsP: 8.5 % (HGG); 13.6 % (DIPG). Two episodes of PsP were based on clinical findings alone; nine episodes had concurrent radiological changes: increased size of lesions (n = 5), new focal enhancement (n = 4). Temozolomide, MGMT methylation or H3F3A mutations were not found to be associated with increased occurrence of PsP. For HGG, 1-year progression-free survival (PFS) was 41.9 % no-PsP versus 100 % PsP (p = 0.041); differences in 1-year overall survival (OS) were not significant. For DIPG, differences in 1-year PFS and OS were not statistically significant. Hazard ratio (95 %CI) of PsP for OS was 0.551 (0.168-1.803; p = 0.325) in HGG; and 0.308 (0.107-0.882; p = 0.028) in DIPG. PsP occurred in both pediatric HGG and DIPG patients at a comparable rate to adult HGG. PsP was associated with improved 1-yr PFS in HGG patients. PsP had a protective effect upon OS in DIPG patients.

Journal Title: Journal of neuro-oncology

PUBMED ID: 27165580

DOI: doi.org/10.1007/s11060-016-2136-7

Titolo: Clinical outcome of an alternative fotemustine schedule in elderly patients with recurrent glioblastoma: a mono-institutional retrospective study.

Autori: Lombardi G., Bellu L., Pambuku A., Della Puppa A., Fiduccia P., Farina M., D'Avella D., Zagonel V.

Data di Pubblicazione: 2016-5-12

Abstract: The optimal treatment of recurrent glioblastoma (GBM) in elderly patients is unclear. Fotemustine (FTM) is a third-generation nitrosourea showing efficacy in gliomas and it has been used with different schedules in adult patients. We performed, for the first time anywhere, a mono-institutional retrospective study to analyze the clinical outcome of an alternative fotemustine schedule in elderly patients with recurrent GBM. Retrospectively, we analyzed all GBM patients 65 years or older previously treated with the combination of radiation therapy and temozolomide (TMZ), receiving an alternative FTM schedule as second-line treatment at our Oncological Center from October 2011 to October 2014 with an ECOG PS  $\leq$  2. FTM was administered at 80 mg/m<sup>2</sup> every 2 weeks for five consecutive administrations (induction phase), and then every 4 weeks at 80 mg/m<sup>2</sup> as maintenance. We enrolled 44 patients, 33 males and 11 females; average age was 70 years. ECOG PS was 0-1 in 80 % of the patients. 38 patients relapsed during temozolomide (TMZ) therapy. MGMT methylation status was analyzed in 34 patients and MGMT was methylated in 53 % of the patients. The median progression free survival (PFS) and overall survival (OS) from FTM treatment was 4.1 months (95 % CI 3.1-5.2) and 7 months (95 % CI 5.2-8.4), respectively. Patients with MGMT methylated status and patients who relapsed after completing TMZ therapy had a longer PFS and OS from the beginning of FTM. Thrombocytopenia was the most frequent grade 3-4 hematological toxicity (9 %). The alternative schedule of FTM may be an active and safe treatment for elderly patients with recurrent glioblastoma, especially patients with methylated MGMT and who relapsed after completing temozolomide therapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 27154166

DOI: doi.org/10.1007/s11060-016-2137-6

Titolo: Update on the evidence-based clinical practice parameter guidelines for the treatment of adults with diffuse low grade glioma: the role of initial chemotherapy.

Autori: Ziu M., Olson JJ.

Data di Pubblicazione: 2016-5-8

Abstract:

Journal Title: Journal of neuro-oncology

PUBMED ID: 27117266

DOI: doi.org/10.1007/s00381-016-3092-4

Titolo: Quantitative imaging analysis of posterior fossa ependymoma location in children.

Autori: Sabin ND., Merchant TE., Li X., Li Y., Klimo P., Boop FA., Ellison DW., Ogg RJ.

Data di Pubblicazione: 2016-4-28

Abstract: Posterior fossa ependymoma can be objectively classified based on quantitative analysis of tumor location, and these classifications are associated with prognostic and treatment factors.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 27108796

DOI: doi.org/10.1016/j.wneu.2016.04.030

Titolo: Progressive Low-Grade Glioma: Assessment of Prognostic Importance of Histologic Reassessment and MRI Findings.

Autori: Narang AK., Chaichana KL., Weingart JD., Redmond KJ., Lim M., Olivi A., Quinones-Hinojosa A., Kleinberg LR.

Data di Pubblicazione: 2016-4-26

Abstract: In patients with progressive LGG, new MRI enhancement and pathologic grade were discordant in greater than 20% of cases. Pathologic confirmation of grade should therefore be attempted, when safe, to dictate management. Beyond functioning as a surrogate for pathologic grade, new MRI enhancement may predict for worse outcomes, a concept that merits prospective investigation.

Journal Title: World neurosurgery

PUBMED ID: 27106406

DOI: doi.org/10.1093/neuonc/now063

Titolo: Restriction spectrum imaging predicts response to bevacizumab in patients with high-grade glioma.

Autori: McDonald CR., Delfanti RL., Krishnan AP., Leyden KM., Hattangadi-Gluth JA., Seibert TM., Karunamuni R., Elbe P., Kuperman JM., Bartsch H., Piccioni DE., White NS., Dale AM., Farid N.

Data di Pubblicazione: 2016-4-24

Abstract: RSI is less influenced by changes in edema, conferring an advantage of RSI over ADC for evaluating response to anti-angiogenic therapy in patients with HGG.

Journal Title: Neuro-oncology

PUBMED ID: 27083133

DOI: doi.org/10.1016/j.jocn.2015.12.028

Titolo: A national perspective of adult gangliogliomas.

Autori: Varshneya K., Sarmiento JM., Nuño M., Lagman C., Mukherjee D., Nuño K., Babu H., Patil CG.

Data di Pubblicazione: 2016-4-17

Abstract: Gangliogliomas (GG) are rare tumors of the nervous system. Patient characteristics and clinical outcomes of low and high-grade GG have been difficult to elucidate in the adult population. This study aims to further elaborate on GG treatment and overall survival utilizing a larger cohort than previously published. The USA National Cancer Database was utilized to evaluate adult (age 18years and older) patients diagnosed with GG between 2004 and 2006. Descriptive statistics and Kaplan-Meier overall survival estimates were provided. A total of 198 adult GG patients were diagnosed between 2004 and 2006. Of these, 181 (91.4%) were low-grade and 17 (8.6%) high-grade GG. Overall, the median age was 36years; approximately 50% of patients were female, and 86.5% Caucasian. Most patients (59%) had near/gross total resection. Radiation and chemotherapy were prescribed in 18 (9.1%) and 11 (5.7%) patients, respectively. Radiation (64.7% versus 3.9%,  $p<.0001$ ) and chemotherapy (47.1% versus 1.7%,  $p<.0001$ ) were more frequently given to patients with high-grade tumors than low-grade. The median overall survival of high-grade GG was 44.4 months (95% confidence interval [CI]: 10.5-92.5) while the corresponding estimate for low-grade tumors was not reached. Older age (hazard ratio [HR] 1.72, 95% CI: 1.26-2.34) and high tumor grade (HR 3.91, 95% CI: 1.43-10.8) were found to be associated with poor survival. Adult GG have a temporal lobe predilection and overall gross total resection rate of 59%. Older patients with high-grade tumors had an increased hazard of mortality. High-grade GG were significantly more likely to be treated with radiation therapy and chemotherapy.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 27082859

DOI: doi.org/10.1159/000445064

Titolo: Optic Pathway Gliomas: Clinical Manifestation, Treatment, and Follow-Up.

Autori: Ertiaei A., Hanaei S., Habibi Z., Moradi E., Nejat F.

Data di Pubblicazione: 2016-4-16

Abstract: OPG occur more commonly in the first decade of life, with visual disturbance as the most prevalent symptom. Tumor staging and the treatment strategy are proposed to affect the response to treatment, although the specific tumor behavior in each patient should be considered as well.

Journal Title: Pediatric neurosurgery

PUBMED ID: 27069431

DOI: doi.org/10.1016/j.jcm.2016.02.004

Titolo: Previously Undiagnosed Malignant Brain Tumor Discovered During Examination of a Patient Seeking Chiropractic Care.

Autori: Anderson B.

Data di Pubblicazione: 2016-4-13

Abstract: This report describes the clinical presentation, examination, and medical management of a 30-year-old man presenting to a chiropractic practice with an unsuspected malignant brain tumor.

Journal Title: Journal of chiropractic medicine

PUBMED ID: 27061921

DOI: doi.org/10.1002/cncr.29987

Titolo: Nonrandomized comparison of neurofibromatosis type 1 and non-neurofibromatosis type 1 children who received carboplatin and vincristine for progressive low-grade glioma: A report from the Children's Oncology Group.

Autori: Ater JL., Xia C., Mazewski CM., Booth TN., Freyer DR., Packer RJ., Sposto R., Vezina G., Pollack IF.

Data di Pubblicazione: 2016-4-11

Abstract: Children with NF1 tolerated CV well and had tumor response rates and EFS that were superior to those for children without NF1. Cancer 2016;122:1928-36. © 2016 American Cancer Society.

Journal Title: Cancer

PUBMED ID: 27057742

DOI: doi.org/10.1159/000443719

Titolo: Clinical Impact of Bevacizumab in Patients with Relapsed Glioblastoma: Focus on a Real-Life Monocentric Survey (SV1 Study).

Autori: Rivoirard R., Chargari C., Guy JB., Nuti C., Peoc'h M., Forest F., Falck AT., Garin C., Adjabi A., Hoarau D., Fotso MJ., Langrand Escure J., Moriceau G., Fournel P., Boutet C., Magné N.

Data di Pubblicazione: 2016-4-9

Abstract: The results of the SV1 study are consistent with those found in phase II studies evaluating the same treatment. The irinotecan-BVZ combination is effective in relapsed glioblastoma with acceptable toxicity. Biomarkers predictive of response to BVZ should help in the selection of patients who could benefit from treatment.

Journal Title: Chemotherapy

PUBMED ID: 27008208

DOI: doi.org/10.1088/0031-9155/61/8/3084

Titolo: Precise image-guided irradiation of small animals: a flexible non-profit platform.

Autori: Tillner F., Thute P., Löck S., Dietrich A., Fursov A., Haase R., Lukas M., Rimarzig B., Sobiella M., Krause M., Baumann M., Bütof R., Enghardt W.

Data di Pubblicazione: 2016-3-24

Abstract: Preclinical in vivo studies using small animals are essential to develop new therapeutic options in radiation oncology. Of particular interest are orthotopic tumour models, which better reflect the clinical situation in terms of growth patterns and microenvironmental parameters of the tumour as well as the interplay of tumours with the surrounding normal tissues. Such orthotopic models increase the technical demands and the complexity of preclinical studies as local irradiation with therapeutically relevant doses requires image-guided target localisation and accurate beam application. Moreover, advanced imaging techniques are needed for monitoring treatment outcome. We present a novel small animal image-guided radiation therapy (SAIGRT) system, which allows for precise and accurate, conformal irradiation and x-ray imaging of small animals. High accuracy is achieved by its robust construction, the precise movement of its components and a fast high-resolution flat-panel detector. Field forming and x-ray imaging is accomplished close to the animal resulting in a small penumbra and a high image quality. Feasibility for irradiating orthotopic models has been proven using lung tumour and glioblastoma models in mice. The SAIGRT system provides a flexible, non-profit academic research platform which can be adapted to specific experimental needs and therefore enables systematic preclinical trials in multicentre research networks.

Journal Title: Physics in medicine and biology

PUBMED ID: 27006178

DOI: doi.org/10.1093/neuonc/nov046

Titolo: Upfront bevacizumab may extend survival for glioblastoma patients who do not receive second-line therapy: an exploratory analysis of AVAglio.

Autori: Chinot O.L., Nishikawa R., Mason W., Henriksson R., Saran F., Cloughesy T., Garcia J., Revil C., Abrey L., Wick W.

Data di Pubblicazione: 2016-3-24

Abstract: This exploratory analysis suggests that the addition of bevacizumab to standard glioblastoma treatment prolongs PFS and OS for patients with PD who receive only one line of therapy.

Journal Title: Neuro-oncology

PUBMED ID: 26994902

DOI: doi.org/10.1007/s11060-016-2109-x

Titolo: Disseminated glioneuronal tumors occurring in childhood: treatment outcomes and BRAF alterations including V600E mutation.

Autori: Dodgshun A.J., SantaCruz N., Hwang J., Ramkissoon S.H., Malkin H., Berghold G., Manley P., Chi S., MacGregor D., Goumnerova L., Sullivan M., Ligon K., Beroukhi R., Herrington B., Kieran M.W., Hansford J.R., Bandopadhyay P.

Data di Pubblicazione: 2016-3-21

Abstract: Disseminated glioneuronal tumors of childhood are rare. We present a retrospective IRB-approved review of the clinical course and frequency of BRAF mutations in disseminated glioneuronal tumors at two institutions. Defining features of our cohort include diffuse leptomeningeal spread, often with a discrete spinal cord nodule and oligodendroglioma-like histologic features. Patients were identified through a pathology database search of all cases with disseminated low-grade neoplasms with an oligodendroglioma-like component. De-identified clinical information was collected by chart review and all imaging was reviewed. We retrieved the results of targeted genomic analyses for alterations in BRAF. Ten patients (aged 2-14 years) were identified from the Dana-Farber/Boston Children's Hospital and the Royal Children's Hospital.

ital, Melbourne pathology databases. Nine patients received chemotherapy. Eight patients are alive, although three have had episodes of progressive disease. We identified genomic alterations affecting the MAPK pathway in six patients. One patient had a germline RAF1 mutation and a clinical diagnosis of cardio-facio-cutaneous syndrome. BRAF duplications were identified in four and BRAF V600E mutation was identified in one. These data support the presence of targetable genomic alterations in this disease.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26992069

DOI: doi.org/10.1002/ajmg.a.37622

Titolo: Histologically benign, clinically aggressive: Progressive non-optic pathway pilocytic astrocytomas in adults with NF1.

Autori: Strowd RE., Rodriguez FJ., McLendon RE., Vredenburg JJ., Chance AB., Jallo G., Olivi A., Ahn ES., Blakeley JO.

Data di Pubblicazione: 2016-3-19

Abstract: Although optic pathway gliomas are the most common brain tumors associated with neurofibromatosis type 1 (NF1), extra-optic gliomas occur and may behave more aggressively with outcomes that differ by age. A retrospective case-control study was designed to describe the clinical course of adult NF1 patients with progressive extra-optic pilocytic astrocytomas (PAs) and compare to a pediatric cohort. Data for patients treated at the Johns Hopkins Comprehensive Neurofibromatosis Center from 2003 to 2013 were reviewed to identify cases (adults, age >18) and controls (pediatric, age <18) with clinically or radiographically progressive extra-optic PAs. Demographic, clinical, histologic, and radiographic data were collected. Three adult NF1 cases and four pediatric NF1 controls were identified. Mean age was 32.3±9.5 years, 66% male (cases); 12.8±4.2 years, 100% male (controls). Symptomatic progression occurred in two-of-three adults (67%) while the majority of pediatric patients presented with isolated radiographic progression (n=3, 75%). Onset tended to be more rapid in adults (4±1 vs. 14±8.3 months, P=0.10). Subtotal resection was the treatment for all pediatric patients. Radiotherapy (n=2), chemotherapy (n=2), and targeted, biologic agents (n=2) were administered in adults. Although all pediatric patients are living, outcomes were universally poor in adults with progression to death in all (median survival 17.1 months, range 6.6-30.3). In conclusion, despite grade I histology, all three adult NF1 patients with progressive extra-optic PAs suffered an aggressive clinical course which was not seen in pediatric patients. Clinicians should be aware of this clinico-histologic discrepancy when counseling and managing adult NF1 patients with progressive extra-optic PAs. © 2016 Wiley Periodicals, Inc.

Journal Title: American journal of medical genetics. Part A

PUBMED ID: 26976201

DOI: doi.org/10.1016/S1470-2045(15)00581-1

Titolo: Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis.

Autori: Thompson EM., Hielscher T., Bouffet E., Remke M., Luu B., Gururangan S., McLendon RE., Bigner DD., Lipp ES., Perreault S., Cho YJ., Grant G., Kim SK., Lee JY., Rao AAN., Giannini C., Li KKW., Ng HK., Yao Y., Kumabe T., Tomiyama T., Grajkowska WA., Perek-Polnik M., Low DCY., Seow WT., Chang KTE., Mora J., Pollack IF., Hamilton RL., Leary S., Moore AS., Ingram WJ., Hallahan AR., Jouvett A., Fèvre-Montange M., Vasiljevic A., Faure-Contier C., Shofuda T., Kagawa N., Hashimoto N., Jabado N., Weil AG., Gayden T., Wataya T., Shalaby T., Grotzer M., Zitterbart K., Sterba J., Kren L., Hortobágyi T., Klekner A., László B., Pócza T., Hauser P., Schüller U., Jung S., Jang WY., French P

J., Kros JM., van Veelen MC., Massimi L., Leonard JR., Rubin JB., Vibhakar R., Chambless LB., Cooper MK., Thompson RC., Faria CC., Carvalho A., Nunes S., Pimentel J., Fan X., Muraszko KM., López-Aguilar E., Lyden D., Garzia L., Shih DJH., Kijima N., Schneider C., Adamski J., Northcott PA., Kool M., Jones DTW., Chan JA., Nikolic A., Garre ML., Van Meir EG., Osuka S., Olson JJ., Jahangiri A., Castro BA., Gupta N., Weiss WA., Moxon-Emre I., Mabbott DJ., Lassaletta A., Hawkins CE., Tabori U., Drake J., Kulkarni A., Dirks P., Rutka JT., Korshunov A., Pfister SM., Packer RJ., Ramaswamy V., Taylor MD.

Data di Pubblicazione: 2016-3-16

Abstract: Canadian Cancer Society Research Institute, Terry Fox Research Institute, Canadian Institutes of Health Research, National Institutes of Health, Pediatric Brain Tumor Foundation, and the Garron Family Chair in Childhood Cancer Research.

Journal Title: The Lancet. Oncology

PUBMED ID: 26970559

DOI: doi.org/10.1002/cncr.29907

Titolo: Clinical and treatment factors determining long-term outcomes for adult survivors of childhood low-grade glioma: A population-based study.

Autori: Krishnatry R., Zhukova N., Guerreiro Stucklin AS., Pole JD., Mistry M., Fried I., Ramaswamy V., Bartels U., Huang A., Laperriere N., Dirks P., Nathan PC., Greenberg M., Malkin D., Hawkins C., Bandopadhyay P., Kieran MW., Manley PE., Bouffet E., Tabori U.

Data di Pubblicazione: 2016-3-13

Abstract: The course of PLGG is associated with excellent long-term survival, but this is hampered by increased delayed mortality in patients receiving upfront radiotherapy. These observations should be considered when treatment options are being weighed for these patients.

Journal Title: Cancer

PUBMED ID: 26947725

DOI: doi.org/10.1016/j.wneu.2016.02.095

Titolo: Primary Intracranial Extra-Axial Anaplastic Ependymomas.

Autori: Yang Y., Tian KB., Hao SY., Wu Z., Li D., Zhang JT.

Data di Pubblicazione: 2016-3-8

Abstract: IEAEs are rare and have a wide spectrum of clinical and radiological phenotypes. Preoperative diagnosis is difficult. Favorable outcomes for IEAEs can be achieved by GTR plus radiotherapy. Multiple IEAEs benefit from tailored staged surgical resection plus radiotherapy.

Journal Title: World neurosurgery

PUBMED ID: 26944115

DOI: doi.org/10.1016/j.jns.2016.01.006

Titolo: Autoimmune atypical parkinsonism - A group of treatable parkinsonism.

Autori: Kanno S., Anandakkuttan A., Mathai A., Sasikumar AN., Nambiar V.

Data di Pubblicazione: 2016-3-6

Abstract: Autoimmune atypical parkinsonism is characterized by atypical parkinsonism with neuronal specific antibodies, sometimes associated with abnormal CSF and significant response to immunotherapy.

Journal Title: Journal of the neurological sciences

PUBMED ID: 26939704

DOI: doi.org/10.1158/1535-7163.MCT-15-0758

Titolo: Entrectinib, a Pan-TRK, ROS1, and ALK Inhibitor with Activity in Multiple Molecularly Defined Cancer Indications.



Autori: Ardini E., Menichincheri M., Banfi P., Bosotti R., De Ponti C., Pulci R., Ballinari D., Ciomei M., Texido G., Degrassi A., Avanzi N., Amboldi N., Saccardo MB., Casero D., Orsini P., Bandiera T., Mologni L., Anderson D., Wei G., Harris J., Vernier JM., Li G., Felder E., Donati D., Isacchi A., Pesenti E., Magnaghi P., Galvani A.

Data di Pubblicazione: 2016-3-5

Abstract: Activated ALK and ROS1 tyrosine kinases, resulting from chromosomal rearrangements, occur in a subset of non-small cell lung cancers (NSCLC) as well as other tumor types and their oncogenic relevance as actionable targets has been demonstrated by the efficacy of selective kinase inhibitors such as crizotinib, ceritinib, and alectinib. More recently, low-frequency rearrangements of TRK kinases have been described in NSCLC, colorectal carcinoma, glioblastoma, and Spitzoid melanoma. Entrectinib, whose discovery and preclinical characterization are reported herein, is a novel, potent inhibitor of ALK, ROS1, and, importantly, of TRK family kinases, which shows promise for therapy of tumors bearing oncogenic forms of these proteins. Proliferation profiling against over 200 human tumor cell lines revealed that entrectinib is exquisitely potent in vitro against lines that are dependent on the drug's pharmacologic targets. Oral administration of entrectinib to tumor-bearing mice induced regression in relevant human xenograft tumors, including the TRKA-dependent colorectal carcinoma KM12, ROS1-driven tumors, and several ALK-dependent models of different tissue origins, including a model of brain-localized lung cancer metastasis. Entrectinib is currently showing great promise in phase I/II clinical trials, including the first documented objective responses to a TRK inhibitor in colorectal carcinoma and in NSCLC. The drug is, thus, potentially suited to the therapy of several molecularly defined cancer settings, especially that of TRK-dependent tumors, for which no approved drugs are currently available. *Mol Cancer Ther*; 15(4); 628-39. ©2016 AACR.

Journal Title: Molecular cancer therapeutics

PUBMED ID: 26934681

DOI: doi.org/10.1002/ijc.30069

Titolo: LOC283731 promoter hypermethylation prognosticates survival after radiochemotherapy in IDH1 wild-type glioblastoma patients.

Autori: Mock A., Geisenberger C., Orlik C., Warta R., Schwager C., Jungk C., Dutruel C., Geiselhart L., Weichenhan D., Zucknick M., Nied AK., Friauf S., Exner J., Capper D., Hartmann C., Lahrmann B., Grabe N., Debus J., von Deimling A., Popanda O., Plass C., Unterberg A., Abdollahi A., Schmezer P., Herold-Mende C.

Data di Pubblicazione: 2016-3-3

Abstract: MGMT promoter methylation status is currently the only established molecular prognosticator in IDH wild-type glioblastoma multiforme (GBM). Therefore, we aimed to discover novel therapy-associated epigenetic biomarkers. After enrichment for hypermethylated fractions using methyl-CpG-immunoprecipitation (MCIP), we performed global DNA methylation profiling for 14 long-term (LTS; >36 months) and 15 short-term (STS; 6-10 months) surviving GBM patients. Even after exclusion of the G-CIMP phenotype, we observed marked differences between the LTS and STS methylome. A total of 1,247 probes in 706 genes were hypermethylated in LTS and 463 probes in 305 genes were found to be hypermethylated in STS patients ( $p$  values < 0.05,  $\log_2$  fold change  $\pm$  0.5). We identified 13 differentially methylated regions (DMRs) with a minimum of four differentially methylated probes per gene. Indeed, we were able to validate a subset of these DMRs through a second, independent method (MassARRAY) in our LTS/STS training set (ADCY1, GPC3, LOC283731/ISLR2). These DMRs were further assessed for their prognostic capability in an independent validation cohort ( $n=62$ ) of non-G-CIMP GBMs from the TCGA. Hypermethylation of multiple CpGs mapping to the promoter region of LOC283731 correlated with improved patient outcome ( $p=0.03$ ). The prognostic performance of LOC283731 promoter hy

permethylation was confirmed in a third independent study cohort (n=89), and was independent of gender, performance (KPS) and MGMT status (p=0.0485, H R=0.63). Intriguingly, the prediction was most pronounced in younger GBM patients (<60 years). In conclusion, we provide compelling evidence that promoter methylation status of this novel gene is a prognostic biomarker in IDH1 wild-type/non-G-CIMP GBMs.

Journal Title: International journal of cancer

PUBMED ID: 26929887

DOI: doi.org/10.7759/cureus.460

Titolo: Long-term Remission Over Six Years for a Patient with Recurrent Glioblastoma Treated with Cediranib/Lomustine.

Autori: Drazin D., Al-Khouja L., Patel A., Hu J., Phuphanich S.

Data di Pubblicazione: 2016-3-2

Abstract: Cediranib is an orally available, pan-VEGFR tyrosine kinase inhibitor. A previous Phase III study of patients with recurrent glioblastoma treated with this drug did not meet the primary end of progressive-free survival (PFS). We identified one patient, a 57-year-old Caucasian female who, following surgery in October 2008 and concurrent temozolomide and radiation therapy from November 8, 2008, to January 6, 2009, developed a tumor progression of the left posterior frontal measuring 1.2 x 1.5 cm in February 2009. She was enrolled in a randomized, Phase III, placebo-controlled, partially-blinded clinical trial of cediranib as either monotherapy or in combination with lomustine (CCNU) versus CCNU. She was randomized to receive a combination therapy with 1st cycle CCNU 190 mg and cediranib 20 mg per day on April 15, 2009. However, she developed nephrotic syndrome and uncontrolled hypertension and was taken off this study in May 2010. Her six-week MRI showed a 50% tumor regression and a complete response at twenty-four weeks. With no enhancement seen on MRI on June 4, 2015, she has been off therapy and in clinical remission over five years with high functional level and good quality of life (KPS-90%). This is a case report of successful therapy for recurrent glioblastoma with long-term remission despite termination of therapy greater than six years from cediranib and limited CCNU dosage.

Journal Title: Cureus

PUBMED ID: 26904576

DOI: doi.org/10.3978/j.issn.2305-5839.2016.01.25

Titolo: Concurrent therapy to enhance radiotherapeutic outcomes in glioblastoma.

Autori: Khosla D.

Data di Pubblicazione: 2016-2-24

Abstract: Glioblastoma is one of the most fatal and incurable human cancers characterized by nuclear atypia, mitotic activity, intense microvascular proliferation and necrosis. The current standard of care includes maximal safe surgical resection followed by radiation therapy (RT) with concurrent and adjuvant temozolomide (TMZ). The prognosis remains poor with median survival of 14.6 months with RT plus TMZ. Majority will have a recurrence within 2 years from diagnosis despite adequate treatment. Radiosensitizers, radiotherapy dose escalation and altered fractionation have failed to improve outcome. The molecular biology of glioblastoma is complex and poses treatment challenges. High rate of mutation, genotypic and phenotypic heterogeneity, rapid development of resistance, existence of blood-brain barrier (BBB), multiple intracellular and intercellular signalling pathways, over-expression of growth factor receptors, angiogenesis and antigenic diversity renders the tumor cells differentially susceptible to various treatment modalities. Thus, the treatment strategies require personalised or individualized approach based on the characteristics of tumor. Several targeted agents have been evaluated in c

linical trials but the results have been modest despite these advancements. This review summarizes the current standard of care, results of concurrent chemoradiation trials, evolving innovative treatments that use targeted therapy with standard chemoradiation or RT alone, outcome of various recent trials and future outlook.

Journal Title: Annals of translational medicine

PUBMED ID: 26885645

DOI: doi.org/10.1371/journal.pone.0149244

Titolo: Safety and Efficacy of 5-Aminolevulinic Acid for High Grade Glioma in Usual Clinical Practice: A Prospective Cohort Study.

Autori: Teixidor P., Arráez MÁ., Villalba G., Garcia R., Tardáguila M., González JJ., Rimbau J., Vidal X., Montané E.

Data di Pubblicazione: 2016-2-18

Abstract: In clinical practice, the 5-ALA showed a good safety profile, but the benefits related to 5-ALA have not been yet clearly shown. The improved differentiation expected by fluorescence between normal and tumor cerebral tissue was suboptimal in a relevant number of patients; in addition, the expected higher degree of resection was lower than in clinical trials as well as incomplete resection was not identified as a prognostic factor risk for death. Because optimal fluorescence was correlated to higher complete resection rate, further research is needed to identify patients (or tumors) with more surgery benefits when using the 5-ALA.

Journal Title: PloS one

PUBMED ID: 26879084

DOI: doi.org/10.1007/s11060-016-2074-4

Titolo: Small increases in enhancement on MRI may predict survival post radiotherapy in patients with glioblastoma.

Autori: Gzell CE., Wheeler HR., McCloud P., Kastelan M., Back M.

Data di Pubblicazione: 2016-2-17

Abstract: To assess impact of volumetric changes in tumour volume post chemoradiotherapy in glioblastoma. Patients managed with chemoradiotherapy between 2008 and 2011 were included. Patients with incomplete MRI sets were excluded. Analyses were performed on post-operative MRI, and MRIs at 1 month (M+1), 3 months (M+3), 5 months (M+5), 7 months (M+7), and 12 months (M+12) post completion of RT. RANO definitions of response were used for all techniques. Modified RANO criteria and two volumetric analysis techniques were used. The two volumetric analysis techniques involved utility of the Eclipse treatment planning software to calculate the volume of delineated tissue: surgical cavity plus all surrounding enhancement (Volumetric) versus surrounding enhancement only (Rim). Retrospective analysis of 49 patients with median survival of 18.4 months. Using Volumetric analysis the difference in MS for patients who had a <5 % increase versus ≥5 % at M+3 was 23.1 versus 15.1 months (p = 0.006), and M+5 was 26.3 versus 15.1 months (p = 0.006). For patients who were classified as progressive disease using modified RANO criteria at M+1 and M+3 there was a difference in MS compared with those who were not (M+1: 13.1 vs. 19.4 months, p = 0.017, M+3: 13.2 vs. 20.1 months, p = 0.096). An increase in the volume of cavity and enhancement of ≥5 % at M+3 and M+5 post RT was associated with reduced survival, suggesting that increases in radiological abnormality of <25 % may predict survival.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26865253

DOI: doi.org/10.1186/s12885-016-2131-6

Titolo: Chemotherapy with BCNU in recurrent glioma: Analysis of clinical outcome and side effects in chemotherapy-naïve patients.

Autori: Jungk C., Chatziaslanidou D., Ahmadi R., Capper D., Bermejo JL., Exner J., von Deimling A., Herold-Mende C., Unterberg A.

Data di Pubblicazione: 2016-2-12

Abstract: In this study, BCNU was rarely associated with severe side effects, particularly pulmonary toxicity, and, in case of recurrent glioblastoma, even conferred a favorable outcome. Therefore BCNU appears to be an appropriate alternative to other nitrosoureas although the efficacy against newer drugs needs further evaluation.

Journal Title: BMC cancer

PUBMED ID: 26853339

DOI: doi.org/10.1016/j.ijrobp.2015.10.032

Titolo: Gemcitabine Plus Radiation Therapy for High-Grade Glioma: Long-Term Results of a Phase 1 Dose-Escalation Study.

Autori: Kim MM., Camelo-Piragua S., Schipper M., Tao Y., Normolle D., Junck L., Mammoser A., Betz BL., Cao Y., Kim CJ., Heth J., Sagher O., Lawrence TS., Tsien CI.

Data di Pubblicazione: 2016-2-9

Abstract: Gemcitabine concurrent with RT is well-tolerated and yields promising outcomes, including in patients with adverse molecular features. It is a candidate for further study, particularly for poor-prognosis patient subgroups with HGG.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 26849840

DOI: doi.org/10.1016/j.clineuro.2016.01.007

Titolo: Local delivery methods of therapeutic agents in the treatment of diffuse intrinsic brainstem gliomas.

Autori: Goodwin CR., Xu R., Iyer R., Sankey EW., Liu A., Abu-Bonsrah N., Sarabia-Estrada R., Frazier JL., Sciubba DM., Jallo GI.

Data di Pubblicazione: 2016-2-6

Abstract: Brainstem gliomas comprise 10-20% of all pediatric central nervous system (CNS) tumors and diffuse intrinsic pontine gliomas (DIPGs) account for the majority of these lesions. DIPG is a rapidly progressive disease with almost universally fatal outcomes and a median survival less than 12 months. Current standard-of-care treatment for DIPG includes radiation therapy, but its long-term survival effects are still under debate. Clinical trials investigating the efficacy of systemic administration of various therapeutic agents have been associated with disappointing outcomes. Recent efforts have focused on improvements in chemotherapeutic agents employed and in methods of localized and targeted drug delivery. This review provides an update on current preclinical and clinical studies investigating treatment options for brainstem gliomas.

Journal Title: Clinical neurology and neurosurgery

PUBMED ID: 26803410

DOI: doi.org/10.1016/j.biomaterials.2016.01.007

Titolo: Fibrin matrices enhance the transplant and efficacy of cytotoxic stem cell therapy for post-surgical cancer.

Autori: Bagó JR., Pegna GJ., Okolie O., Hingtgen SD.

Data di Pubblicazione: 2016-1-25

Abstract: Tumor-homing cytotoxic stem cell (SC) therapy is a promising new approach for treating the incurable brain cancer glioblastoma (GBM). However, problems of retaining cytotoxic SCs within the post-surgical GBM resection cavity are likely to significantly limit the clinical utility of this strategy. Here, we describe a new fibrin-based transplant approach capable of increasing cytotoxic SC retention and persistence within the resection cavity, ye

t remaining permissive to tumorigenic migration. This fibrin-based transplant can effectively treat both solid and post-surgical human GBM in mice. Using our murine model of image-guided model of GBM resection, we discovered that suspending human mesenchymal stem cells (hMSCs) in a fibrin matrix increased initial retention in the surgical resection cavity 2-fold and prolonged persistence in the cavity 3-fold compared to conventional delivery strategies. Time-lapse motion analysis revealed that cytotoxic hMSCs in the fibrin matrix remain tumorigenic, rapidly migrating from the fibrin matrix to co-localize with cultured human GBM cells. We encapsulated hMSCs releasing the cytotoxic agent TRAIL (hMSC-sTR) in fibrin, and found hMSC-sTR/fibrin therapy reduced the viability of multiple 3-D human GBM spheroids and regressed established human GBM xenografts 3-fold in 11 days. Mimicking clinical therapy of surgically resected GBM, intra-cavity seeding of therapeutic hMSC-sTR encapsulated in fibrin reduced post-surgical GBM volumes 6-fold, increased time to recurrence 4-fold, and prolonged median survival from 15 to 36 days compared to control-treated animals. Fibrin-based SC therapy could represent a clinically compatible, viable treatment to suppress recurrence of post-surgical GBM and other lethal cancer types.

Journal Title: Biomaterials

PUBMED ID: 26792581

DOI: doi.org/10.1007/s10637-015-0320-9

Titolo: A dose escalating phase I study of GLPG0187, a broad spectrum integrin receptor antagonist, in adult patients with progressive high-grade glioma and other advanced solid malignancies.

Autori: Cirkel GA., Kerklaan BM., Vanhoutte F., Van der Aa A., Lorenzon G., Namour F., Pujuguet P., Darquenne S., de Vos FY., Snijders TJ., Voest EE., Schellens JH., Lolkema MP.

Data di Pubblicazione: 2016-1-22

Abstract: GLPG0187 was well tolerated with a dose-proportional PK profile upon continuous infusion. No formal maximal tolerated dose could be established. GLPG0187 showed signs of target engagement with a favourable toxicity profile. However, continuous infusion of GLPG0187 failed to show signs of monotherapy efficacy.

Journal Title: Investigational new drugs

PUBMED ID: 26750130

DOI: doi.org/10.1007/s11910-015-0615-4

Titolo: Current Management of Adult Diffuse Infiltrative Low Grade Gliomas.

Autori: Le Rhun E., Taillibert S., Chamberlain MC.

Data di Pubblicazione: 2016-1-12

Abstract: Diffuse infiltrative low grade gliomas (LGG) account for approximately 15 % of all gliomas. The prognosis of LGG differs between high-risk and low-risk patients notwithstanding varying definitions of what constitutes a high-risk patient. Maximal safe resection optimally is the initial treatment. Surgery that achieves a large volume resection improves both progression-free and overall survival. Based on results of three randomized clinical trials (RCT), radiotherapy (RT) may be deferred in patients with low-risk LGG (defined as age <40 years and having undergone a complete resection), although combined chemoradiotherapy has never been prospectively evaluated in the low-risk population. The recent RTOG 9802 RCT established a new standard of care in high-risk patients (defined as age >40 years or incomplete resection) by demonstrating a nearly twofold improvement in overall survival with the addition of PCV (procarbazine, CCNU, vincristine) chemotherapy following RT as compared to RT alone. Chemotherapy alone as a treatment of LGG may result in less toxicity than RT; however, this has only been prospectively studied once (EORTC 22033) in high-risk patients. A challenge remains to define when an aggressive treatment improves survival without impacting quality of life (Qo

L) or neurocognitive function and when an effective treatment can be delayed in order to preserve QoL without impacting survival. Current WHO histopathological classification is poorly predictive of outcome in patients with LGG. The integration of molecular biomarkers with histology will lead to an improved classification that more accurately reflects underlying tumor biology, prognosis, and hopefully best therapy.

Journal Title: Current neurology and neuroscience reports

PUBMED ID: 26711384

DOI: Mancante

Titolo: [Randomized controlled study of limited margins IMRT and temozolomide chemotherapy in patients with malignant glioma].

Autori: Zhang W., Sun J., Cao Y., Yang X.

Data di Pubblicazione: 2015-12-30

Abstract: Both groups gained favorable results, and limited margins doesn't increase local failures. Surgery results are important prognostic factors to immediate-term prognosis and PFS-1.

Journal Title: Zhonghua yi xue za zhi

PUBMED ID: 26671314

DOI: doi.org/10.1016/j.jocn.2015.05.047

Titolo: Multiple resections and survival of recurrent glioblastoma patients in the temozolomide era.

Autori: Ortega A., Sarmiento JM., Ly D., Nuño M., Mukherjee D., Black KL., P atil CG.

Data di Pubblicazione: 2015-12-17

Abstract: Glioblastoma (GBM) is the most prevalent and aggressive primary brain tumor in adults for which recurrence is inevitable and surgical resection is often recommended. We investigated the relationship between multiple tumor resections and overall survival (OS) in adult glioblastoma patients who received adjuvant radiotherapy and temozolomide following initial surgery. We retrospectively reviewed the records of all newly diagnosed adult GBM patients with tumor recurrence at our institution from March 2003 to October 2012. Kaplan-Meier survival estimates and multivariate analysis using Cox's proportional hazards model were utilized to evaluate the impact of multiple resections on OS. A total of 202 GBM patients were analyzed; 83 (41.1%), 94 (46.5%), and 25 (12.4%) patients underwent one, two, and three or more total resections, respectively. Patients who underwent multiple resections were significantly younger ( $p < 0.0001$ ) and had higher perioperative Karnofsky Performance Status scores ( $p < 0.0001$ ) than single resection patients. The median OS in months was 21.1, 25.5, and 29.0 for patients who had one, two, and three or more resections, respectively (Wilcoxon  $p = 0.03$ ). In a confounder-adjusted multivariate model, patients with multiple resections did not have significantly improved survival ( $p = 0.55$ ). Older age was strongly associated with poorer OS (hazard ratio 1.34,  $p < 0.0001$ ). Age at diagnosis was the only predictor of survival for recurrent GBM patients. After adjusting for age at diagnosis, multiple resections were not an independent predictor of OS in our glioblastoma cohort treated in the temozolomide era.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 26659583

DOI: doi.org/10.1007/s00280-015-2927-0

Titolo: Hydroxyurea with or without imatinib in the treatment of recurrent or progressive meningiomas: a randomized phase II trial by Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO).

Autori: Mazza E., Brandes A., Zanon S., Eoli M., Lombardi G., Faedi M., Franceschi E., Reni M.

Data di Pubblicazione: 2015-12-15

Abstract: The conduction of a study in recurrent or progressive meningioma remains a challenge. Given the limited number of patients enrolled, no firm conclusions can be drawn about the combination of imatinib and HU. The optimal systemic therapy for meningioma failing surgery and radiation has yet to be identified.

Journal Title: Cancer chemotherapy and pharmacology

PUBMED ID: 26632856

DOI: doi.org/10.1667/RR14185.1

Titolo: MicroRNA-145 Modulates Tumor Sensitivity to Radiation in Prostate Cancer.

Autori: Gong P., Zhang T., He D., Hsieh JT.

Data di Pubblicazione: 2015-12-4

Abstract: Radiation therapy prior to surgery has increasingly become the standard of care for locally advanced prostate cancer, however tumor radioresistance remains a major clinical problem. While restoration of microRNA-145 (miR-145) expression reduces chemoradioresistance in glioblastoma and suppress prostate cancer proliferation, migration and invasion, the role of miR-145 in response to radiation therapy for prostate cancer is still unknown. The aim of this study was to investigate the role of miR-145 in determining the tumor response to radiation treatment in prostate cancer. Human prostate cancer cells LNCAP and PC3 were transfected with miR-145 mimic. Clonogenic assay was used to determine whether overexpression of miR-145 could alter radiation response in vitro. Immunofluorescence of  $\gamma$ -H2AX and flow cytometric analysis of phosphorylated histone H3 were performed to investigate the potential mechanisms contributing to the enhanced radiation-induced cell killing induced by miR-145. In addition, a qPCR-based array was used to detect the possible miR-145-mediated regulated genes involved. Tumor growth delay assays and survival curves were then analyzed in an animal model to investigate whether miR-145 induced radiosensitivity in vivo. Furthermore, miR-145 expression was assessed in 30 prostate tumor tissue biopsies taken prior to neoadjuvant radiotherapy using miRNA arrays. Our current study suggested that ectopic expression of miR-145 significantly sensitized prostate cancer cells to radiation and we used  $\gamma$ -H2AX phosphorylation as a surrogate marker of radiotherapy response versus miR-145 expression levels. We observed significantly more foci per cell in the group treated with miR-145 and radiation. In addition, mitotic catastrophe was significantly increased in cells receiving miR-145 and radiation. The above results suggest that miR-145 appears to reduce the efficiency of the repair of radiation-induced DNA double-strand breaks in cells. A detailed examination of the involvement of the DNA repair pathway showed that miR-145 reduced the expression of 10 genes involved in DNA repair according to a qPCR-based array data. Irradiation of subcutaneous PC3 tumors in mice treated with R11-miR-145 (a cellular permeable peptide, previously reported) resulted in an increase in radiation-induced tumor growth delay and lived the longest after combination treatment. Moreover, miR-145 expression was significantly increased in patients demonstrating good response (PSA < 2.0 ng/ml/year) to neoadjuvant radiotherapy, while expression of the miR-145-regulated DNA repair genes was significantly decreased. In conclusion, these data suggest a possible mechanism for miR-145 radiosensitivity, potentially through down regulating of DNA repair. This novel study shows a role for miR-145 in modulating radiosensitivity in vivo and highlights the need for further study investigating the potential role of miR-145 as both a predictive marker of response and a novel therapeutic agent with which to enhance the efficacy of radiation therapy.

Journal Title: Radiation research

PUBMED ID: 26626490

DOI: doi.org/10.1007/s11060-015-2008-6

Titolo: A pilot study of bevacizumab-based therapy in patients with newly diagnosed high-grade gliomas and diffuse intrinsic pontine gliomas.

Autori: Hummel TR., Salloum R., Drissi R., Kumar S., Sobo M., Goldman S., Pai A., Leach J., Lane A., Pruitt D., Sutton M., Chow LM., Grimme L., Doughman R., Backus L., Miles L., Stevenson C., Fouladi M., DeWire M.

Data di Pubblicazione: 2015-12-3

Abstract: Although bevacizumab has not proven effective in adults with newly diagnosed high-grade gliomas (HGG), feasibility in newly diagnosed children with diffuse intrinsic pontine gliomas (DIPG) or HGG has not been reported in a prospective study. In a safety and feasibility study, children and young adults with newly diagnosed HGG received radiotherapy (RT) with bevacizumab (10 mg/kg: days 22, 36) and temozolomide (75-90 mg/m<sup>2</sup>/day for 42 days) followed by bevacizumab (10 mg/kg, days 1, 15), irinotecan (125 mg/m<sup>2</sup>, days 1, 15) and temozolomide (150 mg/m<sup>2</sup>/day days 1-5). DIPG patients did not receive temozolomide. Telomerase activity, quality of life (QOL), and functional outcomes were assessed. Among 27 eligible patients (15 DIPG, 12 HGG), median age 10 years (range 3-29 years), 6 discontinued therapy for toxicity: 2 during RT (grade 4 thrombocytopenia, grade 3 hepatotoxicity) and 4 during maintenance therapy (grade 3: thrombosis, hypertension, skin ulceration, and wound dehiscence). Commonest ≥grade 3 toxicities included lymphopenia, neutropenia and leukopenia. Grade 3 hypertension occurred in 2 patients. No intracranial hemorrhages occurred. For DIPG patients, median overall survival (OS) was 10.4 months. For HGG patients, 3-year progression free survival and OS were 33 % (SE ± 14 %) and 50 % (SE ± 14 %), respectively. All 3 tested tumor samples, demonstrated histone H3.3K27M (n = 2 DIPG) or G34R (n = 1 HGG) mutations. QOL scores improved over the course of therapy. A bevacizumab-based regimen is feasible and tolerable in newly diagnosed children and young adults with HGG and DIPG.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26617320

DOI: doi.org/10.1016/j.jneumeth.2015.11.008

Titolo: Chronic, intermittent convection-enhanced delivery devices.

Autori: Lewis O., Woolley M., Johnson D., Rosser A., Barua NU., Bienemann AS., Gill SS., Evans S.

Data di Pubblicazione: 2015-12-1

Abstract: Here we review the improvements that have been made to CED devices over recent years and current state of the art for chronic infusion systems.

Journal Title: Journal of neuroscience methods

PUBMED ID: 26574999

DOI: doi.org/10.1097/CAD.0000000000000314

Titolo: Phase II trial of irinotecan and metronomic temozolomide in patients with recurrent glioblastoma.

Autori: Reynés G., Martínez-Sales V., Vila V., Balañá C., Pérez-Segura P., Vaz MA., Benavides M., Gallego O., Palomero I., Gil-Gil M., Fleitas T., Reche E.

Data di Pubblicazione: 2015-11-18

Abstract: This phase II study was conducted to determine the efficacy and safety of metronomic temozolomide (TMZ) in combination with irinotecan in glioblastoma (GB) at first relapse. Patients with GB at first relapse received TMZ 50 mg/m<sup>2</sup>/day divided into three doses, except for a single 100 mg/m<sup>2</sup> dose, administered between 3 and 6 h before every irinotecan infusion. Irinotecan was given intravenously at the previously established dose of 100 mg/m<sup>2</sup> on days 8 and 22 of 28-day cycles. Treatment was given for a maximum of nine cycles.



cles or until progression or unacceptable toxicity occurred. Vascular endothelial growth factor and its soluble receptor 1, thrombospondin-1, microparticles, and microparticle-dependent procoagulant activity were measured in blood before treatment. The primary objective was 6-month progression-free survival (PFS). Twenty-seven evaluable patients were enrolled. Six-month PFS was 20.8%. Median PFS was 11.6 weeks (95% confidence interval: 7.5-15.7). Stable disease was the best response for nine (37.5%) patients, with a median duration of 11.2 weeks (4.2-35.85 weeks). No differences in PFS or response were observed among patients who relapsed during or after completion of adjuvant TMZ. Grade 3/4 adverse events included lymphopenia (15%), fatigue, diarrhea and febrile neutropenia (3.7% each), lymphopenia, neutropenia, and nausea/vomiting (11.1% each). One patient died from pneumonia and one patient died from pulmonary thromboembolism. Pretreatment levels of angiogenesis biomarkers, microparticles, and microparticle-related procoagulant activity were elevated in patients compared with healthy volunteers. This regimen is feasible, but failed to improve the results obtained with other second-line therapies in recurrent GB.

Journal Title: Anti-cancer drugs

PUBMED ID: 26547911

DOI: doi.org/10.1007/s11060-015-1975-y

Titolo: Seizure reduction is a prognostic marker in low-grade glioma patients treated with temozolomide.

Autori: Koekkoek JA., Dirven L., Heimans JJ., Postma TJ., Vos MJ., Reijneveld JC., Taphoorn MJ.

Data di Pubblicazione: 2015-11-9

Abstract: We aimed to analyze the value of seizure reduction and radiological response as prognostic markers of survival in patients with low-grade glioma (LGG) treated with temozolomide (TMZ) chemotherapy. We retrospectively reviewed adult patients with a progressive LGG and uncontrolled epilepsy in two hospitals (VUmc Amsterdam; MCH The Hague), who received chemotherapy with TMZ between 2002 and 2014. End points were a  $\geq 50$  % seizure reduction and MRI response 6, 12 and 18 months (mo) after the start of TMZ, and their relation with progression-free survival (PFS) and overall survival (OS). We identified 53 patients who met the inclusion criteria. Seizure reduction was an independent prognostic factor for both PFS (HR 0.38; 95 % CI 0.19-0.73;  $p = 0.004$ ) and OS (HR 0.39; 95 % CI 0.18-0.85;  $p = 0.018$ ) after 6mo, adjusting for age and histopathological diagnosis, as well as after 12 and 18mo. Patients with an objective radiological response showed a better OS (median 87.5mo; 95 % CI 62.0-112.9) than patients without a response (median 34.4mo; 95 % CI 26.1-42.6;  $p = 0.046$ ) after 12mo. However, after 6 and 18mo OS was similar in patients with and without a response on MRI. Seizure reduction is an early and consistent prognostic marker for survival after treatment with TMZ, that seems to precede the radiological response. Therefore, seizure reduction may serve as a surrogate marker for tumor response.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26530266

DOI: doi.org/10.1007/s11060-015-1948-1

Titolo: The role of radiotherapy in the management of patients with diffuse low grade glioma: A systematic review and evidence-based clinical practice guideline.

Autori: Ryken TC., Parney I., Buatti J., Kalkanis SN., Olson JJ.

Data di Pubblicazione: 2015-11-5

Abstract: OUTCOMES IN ADULT PATIENTS WITH NEWLY DIAGNOSED LOW GRADE GLIOMA TREATED WITH RADIOTHERAPY: Level I Radiotherapy is recommended in the management of newly diagnosed low-grade glioma in adults to prolong progression free survival, irrespective of extent of resection. Level II Radiotherapy is re

commended in the management of newly diagnosed low grade glioma in adults as an equivalent alternative to observation in preserving cognitive function, irrespective of extent of resection. Level III Radiotherapy is recommended in the management of newly diagnosed low grade glioma in adults to improve seizure control in patients with epilepsy and subtotal resection. Level III Radiotherapy is recommended in the management of newly diagnosed low-grade glioma in adults to prolong overall survival in patients with subtotal resection. Level III Consideration of the risk of radiation induced morbidity, including cognitive decline, imaging abnormalities, metabolic dysfunction and malignant transformation, is recommended when the delivery of radiotherapy is selected in the management of newly diagnosed low-grade glioma in adults. STRATEGIES OF RADIOTHERAPY IN ADULT PATIENTS WITH NEWLY DIAGNOSED LOW GRADE GLIOMA: Level I Lower dose radiotherapy is recommended as an equivalent alternative to higher dose immediate postoperative radiotherapy (45-50.4 vs. 59.4-64.8 Gy) in the management of newly diagnosed low-grade glioma in adults with reduced toxicity. Level III Delaying radiotherapy until recurrence or progression is recommended as an equivalent alternative to immediate postoperative radiotherapy in the management of newly diagnosed low-grade glioma in adults but may result in shorter time to progression. Level III The addition of chemotherapy to radiotherapy is not recommended over whole brain radiotherapy alone in the management of low-grade glioma, as it provides no additional survival benefit. Level III Limited-field radiotherapy is recommended over whole brain radiotherapy in the management of low-grade glioma. Level III Either stereotactic radiosurgery or brachytherapy are recommended as acceptable alternatives to external radiotherapy in selected patients. PROGNOSTIC FACTORS IN ADULT PATIENTS WITH NEWLY DIAGNOSED LOW GRADE GLIOMA TREATED WITH RADIOTHERAPY: Level II It is recommended that age greater than 40 years, astrocytic pathology, diameter greater than 6 cm, tumor crossing the midline and preoperative neurological deficit be considered as negative prognostic indicators when predicting overall survival in adult low grade glioma patients treated with radiotherapy. Level II It is recommended that smaller tumor size, extent of surgical resection and higher mini-mental status exam be considered as positive prognostic indicators when predicting overall survival and progression free survival in patients in adult low grade glioma patients treated with radiotherapy. Level III It is recommended that seizures at presentation, presence of oligodendroglial histological component and 1p19q deletion (along with additional relevant factors-see Table 1) be considered as positive prognostic indicators when predicting response to radiotherapy in adults with low grade gliomas. Level III It is recommended that increasing age, decreasing performance status, decreasing cognition, presence of astrocytic histological component (along with additional relevant factors (see Tables 1, 2) be considered as negative prognostic indicators when predicting response to radiotherapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26530265

DOI: doi.org/10.1007/s11060-015-1867-1

Titolo: The role of surgery in the management of patients with diffuse low grade glioma: A systematic review and evidence-based clinical practice guideline.

Autori: Aghi MK., Nahed BV., Sloan AE., Ryken TC., Kalkanis SN., Olson JJ.

Data di Pubblicazione: 2015-11-5

Abstract: Intraoperative mapping is recommended for patients with diffuse LGGs in eloquent locations compared to patients with non-eloquently located diffuse LGGs as a way of preserving function.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26530264

DOI: doi.org/10.1007/s11060-015-1910-2

Titolo: Management of patients with recurrence of diffuse low grade glioma: A systematic review and evidence-based clinical practice guideline.

Autori: Nahed BV., Redjal N., Brat DJ., Chi AS., Oh K., Batchelor TT., Ryken TC., Kalkanis SN., Olson JJ.

Data di Pubblicazione: 2015-11-5

Abstract: There is insufficient evidence to make any specific recommendation s. It is recommended that individuals with recurrent LGGs be enrolled in a properly designed clinical trial to assess the role of surgery at recurrence.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26530261

DOI: doi.org/10.1007/s11060-015-1931-x

Titolo: The role of initial chemotherapy for the treatment of adults with diffuse low grade glioma : A systematic review and evidence-based clinical practice guideline.

Autori: Ziu M., Kalkanis SN., Gilbert M., Ryken TC., Olson JJ.

Data di Pubblicazione: 2015-11-5

Abstract: Level II: It is recommended that chemotherapy be added to the RT in patients with unfavorable LGG to improve their progression free survival.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26526984

DOI: doi.org/10.1007/s00280-015-2895-4

Titolo: Phase 1 study of galunisertib, a TGF-beta receptor I kinase inhibitor, in Japanese patients with advanced solid tumors.

Autori: Fujiwara Y., Nokihara H., Yamada Y., Yamamoto N., Sunami K., Utsumi H., Asou H., Takahashi O., Ogasawara K., Gueorguieva I., Tamura T.

Data di Pubblicazione: 2015-11-4

Abstract: NCT01722825.

Journal Title: Cancer chemotherapy and pharmacology

PUBMED ID: 26501997

DOI: doi.org/10.1002/ijc.29898

Titolo: A concurrent ultra-fractionated radiation therapy and temozolomide treatment: A promising therapy for newly diagnosed, inoperable glioblastoma.

Autori: Beauchesne P., Quillien V., Faure G., Bernier V., Noel G., Quetin P., Gorlia T., Carnin C., Pedoux R.

Data di Pubblicazione: 2015-10-27

Abstract: We report on a phase II clinical trial to determine the effect of a concurrent ultra-fractionated radiotherapy and temozolomide treatment in inoperable glioblastoma patients. A phase II study opened; patients over 18 years of age who were able to give informed consent and had histologically proven, newly diagnosed inoperable diagnosed and supratentorial glioblastoma were eligible. Three doses of 0.75 Gy spaced apart by at least 4 hr were delivered daily, 5 days a week for six consecutive weeks for a total of 67.5 Gy. Chemotherapy was administered during the same period, which consisted of temozolomide given at a dose of 75 mg/m<sup>2</sup> for 7 days a week. After a 4-week break, chemotherapy was resumed for up to six cycles of adjuvant temozolomide treatment, given every 28 days, according to the standard 5-day regimen. Tolerance and toxicity were the primary endpoints; survival and progression-free survival were the secondary endpoints. In total, 40 patients were enrolled in this study, 29 men and 11 women. The median age was 58 years, and the median Karnofsky performance status was 80. The concomitant ultra-fractionated radiotherapy and temozolomide treatment was well tolerated. Complete responses were seen in four patients, and partial responses were reported in seven patients. The median survival from the initial diagnosis was 16 months. Seve

ral long-term survivors were noted. Concurrent ultra-fractionated radiation therapy and temozolomide treatment are well accepted by the patients. The results showed encouraging survival rates for these unfavorable patients.  
Journal Title: International journal of cancer

PUBMED ID: 26496463

DOI: doi.org/10.1159/000440678

Titolo: Carboplatin and Etoposide in Heavily Pretreated Patients with Progressive High-Grade Glioma.

Autori: Tonder M., Weller M., Eisele G., Roth P.

Data di Pubblicazione: 2015-10-27

Abstract: Carboplatin in combination with etoposide has an unfavorable risk-benefit profile in heavily pretreated glioma patients.

Journal Title: Chemotherapy

PUBMED ID: 26487690

DOI: doi.org/10.1093/neuonc/nov256

Titolo: Apparent diffusion coefficient histogram metrics correlate with survival in diffuse intrinsic pontine glioma: a report from the Pediatric Brain Tumor Consortium.

Autori: Poussaint TY., Vajapeyam S., Ricci KI., Panigrahy A., Kocak M., Kuntz LE., Boyett JM., Pollack IF., Fouladi M.

Data di Pubblicazione: 2015-10-22

Abstract: ADC histogram metrics in DIPG demonstrate significant correlations between diffusion metrics and survival, with lower diffusion values (increased cellularity), increased skewness, and enhancement associated with shorter survival, requiring future investigations in large DIPG clinical trials.

Journal Title: Neuro-oncology

PUBMED ID: 26474099

DOI: doi.org/10.3171/2015.6.PEDS15166

Titolo: Malignant brainstem tumors in children, excluding diffuse intrinsic pontine gliomas.

Autori: Klimo P., Nesvick CL., Broniscer A., Orr BA., Choudhri AF.

Data di Pubblicazione: 2015-10-17

Abstract: OBJECT Malignant tumors of the brainstem, excluding classic diffuse intrinsic pontine gliomas (DIPGs), are a very rare, heterogeneous group of neoplasms that have been infrequently described in the literature. In this paper, the authors present their experiences with treating these unique cancers. METHODS A retrospective chart review was conducted to identify eligible cases over a 15-year period. All tumors involving the pons were, by consensus, felt not to be DIPGs based on their neuroimaging features. Demographic information, pathological specimens, neuroimaging characteristics, surgical and nonsurgical management plans, and survival data were gathered for analysis. RESULTS Between January 2000 and December 2014, 29 patients were identified. The mean age at diagnosis was 8.4 years (range 2 months to 25 years), and 17 (59%) patients were male. The most common presenting signs and symptoms were cranial neuropathies (n = 24; 83%), hemiparesis (n = 12; 41%), and ataxia or gait disturbance (n = 10; 34%). There were 18 glial and 11 embryonal tumors. Of the glial tumors, 5 were radiation-induced and 1 was a malignant transformation of a previously known low-grade tumor. Surgical intervention consisted of biopsy alone in 12 patients and some degree of resection in another 15 patients. Two tumors were diagnosed postmortem. The median overall survival for all patients was 196 days (range 15 to 3999 days). There are currently 5 (17%) patients who are still alive: 1 with an anaplastic astrocytoma and the remaining with embryonal tumors. CONCLUSIONS In general, malignant non-DIPG tumors of the brainstem carry a poor prognosis. However, maximal cyt

oreductive surgery may be an option for select patients with focal tumors. Long-term survival is possible in patients with nonmetastatic embryonal tumors after multimodal treatment, most importantly maximal resection.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 26468139

DOI: doi.org/10.1007/s11060-015-1955-2

Titolo: Myxopapillary ependymomas in children: imaging, treatment and outcomes.

Autori: Bandopadhyay P., Silvera VM., Ciarlini PDSC., Malkin H., Bi WL., Bergthold G., Faisal AM., Ullrich NJ., Marcus K., Scott RM., Beroukhim R., Manley PE., Chi SN., Ligon KL., Goumnerova LC., Kieran MW.

Data di Pubblicazione: 2015-10-16

Abstract: Myxopapillary ependymomas (MPEs) are rare spinal tumors in children. The natural history and clinical course of pediatric MPEs are largely unknown and the indication for adjuvant therapy remains to be clarified. We performed an IRB-approved, retrospective review of children with MPEs treated at the Dana-Farber/Boston Children's Cancer and Blood Disorder Center between 1982 and 2013. Eighteen children (age range 8-21 years, median age 14 years) met inclusion criteria. We reviewed the histopathology, magnetic resonance imaging, tumor location and stage, surgical management, adjuvant therapy, and clinical outcomes. The median follow-up duration was 9.4 years (range 1-30 years). Children most commonly presented with pain, scoliosis, and urinary symptoms. All primary tumors were located in the lower thoracic or lumbar spine. Nine children (50%) had leptomeningeal tumor seeding at presentation, most commonly located within the distal thecal sac. A gross-total resection was achieved in nine children (50%). Three children were treated with irradiation following initial surgery. No child received adjuvant chemotherapy at diagnosis. The 10-year event-free survival (EFS) was  $26\% \pm 14.8$ . Children with disseminated disease trended towards inferior EFS compared to those with localized disease (10-year EFS  $12.7\% \pm 12$  vs.  $57 \pm 25\%$ , p value 0.07). The 10-year overall survival was 100%. The efficacy of adjuvant irradiation could not be assessed due to the small sample size. Although children with MPEs frequently present with disseminated tumor and/or develop recurrent or progressive disease, their overall survival is excellent. Treatment should aim to minimize both tumor- and therapy-related morbidity.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26451615

DOI: doi.org/10.18632/oncotarget.5437

Titolo: The radiosensitivity index predicts for overall survival in glioblastoma.

Autori: Ahmed KA., Chinnaiyan P., Fulp WJ., Eschrich S., Torres-Roca JF., Caudell JJ.

Data di Pubblicazione: 2015-10-10

Abstract: We have previously developed a multigene expression model of tumor radiosensitivity (RSI) with clinical validation in multiple cohorts and disease sites. We hypothesized RSI would identify glioblastoma patients who would respond to radiation and predict treatment outcomes. Clinical and array based gene expression (Affymetrix HT Human Genome U133 Array Plate Set) level 2 data was downloaded from the cancer genome atlas (TCGA). A total of 270 patients were identified for the analysis: 214 who underwent radiotherapy and temozolomide and 56 who did not undergo radiotherapy. Median follow-up for the entire cohort was 9.1 months (range: 0.04-92.2 months). Patients who did not receive radiotherapy were more likely to be older ( $p < 0.001$ ) and of poorer performance status ( $p < 0.001$ ). On multivariate analysis, RSI is an independent predictor of OS (HR = 1.64, 95% CI 1.08-2.5;  $p = 0.02$ ). Furthermore, on subset analysis, radiosensitive patients had significantly improved OS in

the patients with high MGMT expression (unmethylated MGMT), 1 year OS 84.1% vs. 53.7% ( $p = 0.005$ ). This observation held on MVA (HR = 1.94, 95% CI 1.19-3.31;  $p = 0.008$ ), suggesting that RT has a larger therapeutic impact in these patients. In conclusion, RSI predicts for OS in glioblastoma. These data further confirm the value of RSI as a disease-site independent biomarker.  
Journal Title: Oncotarget

PUBMED ID: 26448943

DOI: doi.org/10.1155/2015/641023

Titolo: The Diagnostic Ability of Follow-Up Imaging Biomarkers after Treatment of Glioblastoma in the Temozolomide Era: Implications from Proton MR Spectroscopy and Apparent Diffusion Coefficient Mapping.

Autori: Bulik M., Kazda T., Slampa P., Jancalek R.

Data di Pubblicazione: 2015-10-9

Abstract: Institutional validation of cut-off values obtained from advanced MRI methods is warranted not only for diagnosis of GBM recurrence, but also as enrollment criteria in salvage clinical trials and for reporting of outcomes of initial treatment.

Journal Title: BioMed research international

PUBMED ID: 26399631

DOI: doi.org/10.1007/s00401-015-1478-0

Titolo: Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes.

Autori: Castel D., Philippe C., Calmon R., Le Dret L., Truffaux N., Boddaert N., Pagès M., Taylor KR., Saulnier P., Lacroix L., Mackay A., Jones C., Sainte-Rose C., Blauwblomme T., Andreiulo F., Puget S., Grill J., Varlet P., Debily MA.

Data di Pubblicazione: 2015-9-25

Abstract: Diffuse intrinsic pontine glioma (DIPG) is the most severe paediatric solid tumour, with no significant therapeutic progress made in the past 50 years. Recent studies suggest that diffuse midline glioma, H3-K27M mutant, may comprise more than one biological entity. The aim of the study was to determine the clinical and biological variables that most impact their prognosis. Ninety-one patients with classically defined DIPG underwent a systematic stereotactic biopsy and were included in this observational retrospective study. Histone H3 genes mutations were assessed by immunohistochemistry and direct sequencing, whilst global gene expression profiling and chromosomal imbalances were determined by microarrays. A full description of the MRI findings at diagnosis and at relapse was integrated with the molecular profiling data and clinical outcome. All DIPG but one were found to harbour either a somatic H3-K27M mutation and/or loss of H3K27 trimethylation. We also discovered a novel K27M mutation in HIST2H3C, and a lysine-to-isoleucine substitution (K27I) in H3F3A, also creating a loss of trimethylation. Patients with tumours harbouring a K27M mutation in H3.3 (H3F3A) did not respond clinically to radiotherapy as well, relapsed significantly earlier and exhibited more metastatic recurrences than those in H3.1 (HIST1H3B/C). H3.3-K27M-mutated DIPG have a proneural/oligodendroglial phenotype and a pro-metastatic gene expression signature with PDGFRA activation, while H3.1-K27M-mutated tumours exhibit a mesenchymal/astrocytic phenotype and a pro-angiogenic/hypoxic signature supported by expression profiling and radiological findings. H3K27 alterations appear as the founding event in DIPG and the mutations in the two main histone H3 variants drive two distinct oncogenic programmes with potential specific therapeutic targets.

Journal Title: Acta neuropathologica

PUBMED ID: 26384811

DOI: doi.org/10.1007/s11060-015-1883-1

Titolo: The use of (18)F-FDG PET to differentiate progressive disease from treatment induced necrosis in high grade glioma.

Autori: Dankbaar JW., Snijders TJ., Robe PA., Seute T., Eppinga W., Hendriks e J., De Keizer B.

Data di Pubblicazione: 2015-9-20

Abstract: In the follow-up of patients treated for high grade glioma, differentiation between progressive disease (PD) and treatment-induced necrosis (TIN) is challenging. The purpose of this study is to evaluate the diagnostic accuracy of FDG PET for the differentiation between TIN and PD after high grade glioma treatment. We retrospectively identified patients between January 2011 and July 2013 that met the following criteria: age >18; glioma grade 3 or 4; treatment with radiotherapy or chemoradiotherapy; new or progressive enhancement on post treatment MRI; FDG PET within 4 weeks of MRI. Absolute and relative (to contralateral white matter) values of SUVmax and SUVpeak were determined in new enhancing lesions on MRI. The outcome of PD or TIN was determined by neurosurgical biopsy/resection, follow-up MRI, or clinical deterioration. The association between FDG PET and outcome was analyzed with univariate logistic regression and ROC analysis for: all lesions, lesions >10, >15, and >20 mm. We included 30 patients (5 grade 3 and 25 grade 4), with 39 enhancing lesions on MRI. Twenty-nine lesions represented PD and 10 TIN. Absolute and relative values of SUVmax and SUVpeak showed no significant differences between PD and TIN. ROC analysis showed highest AUCs for relative SUVpeak in all lesion sizes. Relative SUVpeak for lesions >20 mm showed reasonable discriminative properties [AUC 0.69 (0.41-0.96)]. FDG PET has reasonable discriminative properties for differentiation of PD from TIN in high grade gliomas larger than 20 mm. Overall diagnostic performance is insufficient to guide clinical decision-making.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26364181

DOI: doi.org/10.1007/s00234-015-1582-9

Titolo: Early biomarkers from dynamic contrast-enhanced magnetic resonance imaging to predict the response to antiangiogenic therapy in high-grade gliomas.

Autori: Piludu F., Marzi S., Pace A., Villani V., Fabi A., Carapella CM., Terrereno I., Antenucci A., Vidiri A.

Data di Pubblicazione: 2015-9-14

Abstract: Tumor subvolumes with increased nIAUGC and K(trans) showed the potential for improving the diagnostic accuracy of DCE. Early assessments of the entire tumor volume, including necrotic areas, may provide complementary information of tumor behavior in response to anti-VEGF therapies and is worth further investigation.

Journal Title: Neuroradiology

PUBMED ID: 26354927

DOI: doi.org/10.1093/neuonc/nov182

Titolo: Molecular classification of anaplastic oligodendroglioma using next-generation sequencing: a report of the prospective randomized EORTC Brain Tumor Group 26951 phase III trial.

Autori: Dubbink HJ., Atmodimedjo PN., Kros JM., French PJ., Sanson M., Idbaih A., Wesseling P., Enting R., Spliet W., Tijssen C., Dinjens WN., Gorlia T., van den Bent MJ.

Data di Pubblicazione: 2015-9-11

Abstract: Targeted NGS allows a clinically relevant classification of diffuse glioma into groups with very different outcomes. The diagnosis of diffuse glioma should be primarily based on a molecular classification, with the histopathological grade added to it. Future discussion should primarily aim at

establishing the minimum requirements for molecular classification of diffuse glioma.

Journal Title: Neuro-oncology

PUBMED ID: 26352098

DOI: doi.org/10.1227/NEU.0000000000001019

Titolo: Spinal Anaplastic Oligodendroglioma With Oligodendrogliomatosis: Molecular Markers and Management: Case Report.

Autori: Strickland BA., Cachia D., Jalali A., Cykowski MD., Penas-Prado M., Langford LA., Li J., Shah K., Weinberg JS.

Data di Pubblicazione: 2015-9-10

Abstract: Management, prognosis, and use of molecular data in the decision-making algorithm for these patients are discussed, together with a review of all cases of primary intradural intramedullary spinal anaplastic oligodendrogliomas reported to date. Our study indicates that the combination of sequential treatment with radiation and temozolomide might provide a favorable outcome in the case of 1p/19q-codeleted spinal anaplastic oligodendrogliomas and that molecular analysis can be beneficial in guiding treatment strategies, although the impact of IDH mutations on these tumors is still unclear.

Journal Title: Neurosurgery

PUBMED ID: 26351224

DOI: doi.org/10.1007/s00381-015-2860-x

Titolo: Pediatric infratentorial ganglioglioma.

Autori: Puget S., Alshehri A., Beccaria K., Blauwblomme T., Paternoster G., James S., Dirocco F., Dufour C., Zerah M., Varlet P., Sainte-Rose C.

Data di Pubblicazione: 2015-9-10

Abstract: Pediatric posterior fossa gangliogliomas are rare and challenging tumors due to their frequent infiltrative component involving the brainstem. To date, adjuvant therapy has a limited role that may evolve with time thanks to the use of targeted therapies against BRAF mutation. The surgical resection of well-defined contrast enhancing parts should be attempted even in staged surgeries and balanced with the risks of neurological deterioration.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 26323606

DOI: doi.org/10.1093/neuonc/nov167

Titolo: Temozolomide as salvage treatment for recurrent intracranial ependymomas of the adult: a retrospective study.

Autori: Rudà R., Bosa C., Magistrello M., Franchino F., Pellerino A., Fiano V., Trevisan M., Cassoni P., Soffietti R.

Data di Pubblicazione: 2015-9-2

Abstract: TMZ has a role in recurrent chemo-naïve adult patients with intracranial ependymoma, regardless of tumor grade and MGMT methylation. We suggest that, after failure of surgery and radiotherapy, TMZ should be considered as a possible first-line treatment for recurrent ependymoma.

Journal Title: Neuro-oncology

PUBMED ID: 26314843

DOI: doi.org/10.18632/oncotarget.4549

Titolo: TERT promoter mutations contribute to IDH mutations in predicting differential responses to adjuvant therapies in WHO grade II and III diffuse gliomas.



Autori: Zhang ZY., Chan AK., Ding XJ., Qin ZY., Hong CS., Chen LC., Zhang X., Zhao FP., Wang Y., Wang Y., Zhou LF., Zhuang Z., Ng HK., Yan H., Yao Y., Mao Y.

Data di Pubblicazione: 2015-8-29

Abstract: IDH mutations frequently occur in WHO grade II and III diffuse gliomas and have favorable prognosis compared to wild-type tumors. However, whether IDH mutations in WHO grade II and III diffuse gliomas predict enhanced sensitivity to adjuvant radiation (RT) or chemotherapy (CHT) is still being debated. Recent studies have identified recurrent mutations in the promoter region of telomerase reverse transcriptase (TERT) in gliomas. We previously demonstrated that TERT promoter mutations may be promising biomarkers in glioma survival prognostication when combined with IDH mutations. This study analyzed IDH and TERT promoter mutations in 295 WHO grade II and III diffuse gliomas treated with or without adjuvant therapies to explore their impact on the sensitivity of tumors to genotoxic therapies. IDH mutations were found in 216 (73.2%) patients and TERT promoter mutations were found in 112 (38%) patients. In multivariate analysis, IDH mutations ( $p < 0.001$ ) were independent prognostic factors for PFS and OS in patients receiving genotoxic therapies while TERT promoter mutations were not. In univariate analysis, IDH and TERT promoter mutations were not significant prognostic factors in patients who did not receive genotoxic therapies. Adjuvant RT and CHT were factors independently impacting PFS (RT  $p = 0.001$ , CHT  $p = 0.026$ ) in IDH mutated WHO grade II and III diffuse gliomas but not in IDH wild-type group. Univariate and multivariate analyses demonstrated TERT promoter mutations further stratified IDH wild-type WHO grade II and III diffuse gliomas into two subgroups with different responses to genotoxic therapies. Adjuvant RT and CHT were significant parameters influencing PFS in the IDH wt/TERT mut subgroup (RT  $p = 0.015$ , CHT  $p = 0.015$ ) but not in the IDH wt/TERT wt subgroup. Our data demonstrated that IDH mutated WHO grade II and III diffuse gliomas had better PFS and OS than their IDH wild-type counterparts when genotoxic therapies were administered after surgery. Importantly, we also found that TERT promoter mutations further stratify IDH wild-type WHO grade II and III diffuse gliomas into two subgroups with different responses to adjuvant therapies. Taken together, TERT promoter mutations may predict enhanced sensitivity to genotoxic therapies in IDH wild-type WHO grade II and III diffuse gliomas and may justify intensified treatment in this subgroup.

Journal Title: Oncotarget

PUBMED ID: 26308501

DOI: doi.org/10.1080/21645515.2015.1081727

Titolo: The progress of immunotherapy for glioblastoma.

Autori: Zhou Q., Wang Y., Ma W.

Data di Pubblicazione: 2015-8-27

Abstract: Glioblastoma is the most common primary brain tumor in adults, accounting for about half of all primary brain tumors. Despite multiple therapeutic interventions such as surgical resection, radiotherapy, and systemic chemotherapy, the prognosis for glioblastoma remains poor. Due to the scientific community's enhanced understanding of the CNS immune system and significant achievements in tumor immunotherapy in recent years, immunotherapy has become a promising GBM treatment. In vaccine therapy, a number of clinical trials have achieved encouraging results. In antibody therapy, antibodies are used to target immune checkpoints such as ipilimumab and nivolumab. Bioengineering technology has also led to a new field of tumor immunotherapy, whereby genetically modified tumor-specific T cells are reintroduced into a patient's body.

Journal Title: Human vaccines & immunotherapeutics

PUBMED ID: 26294320

DOI: doi.org/10.1007/s00520-015-2897-0

Titolo: Validating self-report and proxy reports of the Dexamethasone Symptom Questionnaire -Chronic for the evaluation of longer-term corticosteroid toxicity.

Autori: Agar M., Koh ES., Gibbs E., Barnes EH., Hovey E., Livingstone A., Salkin K., Chye R., Lovell MR., Clark K., Vardy J., King M., King M.

Data di Pubblicazione: 2015-8-22

Abstract: The DSQ-Chronic is feasible when the patient is relatively well. As capacity to complete the DSQ-Chronic diminishes, caregivers can be proxy-raters. Clinicians capture corticosteroid toxicities, which may not be obvious to the patient. The DSQ-Chronic, patient and caregiver versions, are useful tools to be used with clinician assessment.

Journal Title: Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer

PUBMED ID: 26289591

DOI: doi.org/10.1093/neuonc/nov152

Titolo: Differentiating the mTOR inhibitors everolimus and sirolimus in the treatment of tuberous sclerosis complex.

Autori: MacKeigan JP., Krueger DA.

Data di Pubblicazione: 2015-8-21

Abstract: Tuberous sclerosis complex (TSC) is a genetic autosomal dominant disorder characterized by benign tumor-like lesions, called hamartomas, in multiple organ systems, including the brain, skin, heart, kidneys, and lung. These hamartomas cause a diverse set of clinical problems based on their location and often result in epilepsy, learning difficulties, and behavioral problems. TSC is caused by mutations within the TSC1 or TSC2 genes that inactivate the genes' tumor-suppressive function and drive hamartomatous cell growth. In normal cells, TSC1 and TSC2 integrate growth signals and nutrient inputs to downregulate signaling to mammalian target of rapamycin (mTOR), an evolutionarily conserved serine-threonine kinase that controls cell growth and cell survival. The molecular connection between TSC and mTOR led to the clinical use of allosteric mTOR inhibitors (sirolimus and everolimus) for the treatment of TSC. Everolimus is approved for subependymal giant cell astrocytomas and renal angiomyolipomas in patients with TSC. Sirolimus, though not approved for TSC, has undergone considerable investigation to treat various aspects of the disease. Everolimus and sirolimus selectively inhibit mTOR signaling with similar molecular mechanisms, but with distinct clinical profiles. This review differentiates mTOR inhibitors in TSC while describing the molecular mechanisms, pathogenic mutations, and clinical trial outcomes for managing TSC.

Journal Title: Neuro-oncology

PUBMED ID: 26282642

DOI: doi.org/10.1200/JCO.2015.61.1525

Titolo: Evaluation of the Safety and Benefit of Phase I Oncology Trials for Patients With Primary CNS Tumors.

Autori: Gounder MM., Nayak L., Sahebjam S., Muzikansky A., Sanchez AJ., Desideri S., Ye X., Ivy SP., Nabors LB., Prados M., Grossman S., DeAngelis LM., Wen PY.

Data di Pubblicazione: 2015-8-19

Abstract: Patients with HGG who meet standard eligibility criteria may be good candidates for solid tumor phase I studies with single-agent molecular or cytotoxic drugs with favorable preclinical rationale and pharmacokinetic properties in this population.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 26254812

DOI: doi.org/10.1016/j.ejca.2015.06.124

Titolo: Metastatic medulloblastoma in adults: outcome of patients treated according to the HIT2000 protocol.

Autori: von Bueren AO., Friedrich C., von Hoff K., Kwiecien R., Müller K., Pietsch T., Warmuth-Metz M., Hau P., Benesch M., Kuehl J., Kortmann RD., Rutkowski S.

Data di Pubblicazione: 2015-8-10

Abstract: Treatment of adults with metastatic medulloblastoma according to the intensified paediatric HIT2000 protocol was feasible with acceptable toxicities. EFS rates achieved by both chemotherapeutic protocols were favourable and appear to be inferior to those obtained in older children/adolescents with metastatic disease.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 26243269

DOI: doi.org/10.1007/s11060-015-1863-5

Titolo: IDH1 mutation is prognostic for diffuse astrocytoma but not low-grade oligodendrogliomas in patients not treated with early radiotherapy.

Autori: Iwade Y., Matsutani T., Hirono S., Ikegami S., Shinozaki N., Saeki N.

Data di Pubblicazione: 2015-8-6

Abstract: Despite accumulating knowledge regarding molecular backgrounds, the optimal management strategy for low-grade gliomas remains controversial. One reason is the marked heterogeneity in the clinical course. To establish an accurate subclassification of low-grade gliomas, we retrospectively evaluated isocitrate dehydrogenase-1 (IDH1) mutation in clinical specimens of diffuse astrocytomas (DA) and oligodendroglial tumors separately. No patients were treated with early radiotherapy, and modified PCV chemotherapy was used for postoperative residual tumors or recurrence in oligodendroglial tumors. Immunohistochemical evaluation of IDH status, p53 status, O(6)-methylguanine methyltransferase expression, and the MIB-1 index were performed. The 1p and 19q status was analyzed with fluorescence in situ hybridization. Ninety-four patients were followed for a median period of 8.5 years. For DAs, p53 was prognostic for progression-free survival (PFS) and IDH1 was significant for overall survival (OS) with multivariate analysis. In contrast, for oligodendroglial tumors, none of the parameters was significant for PFS or OS. Thus, the significance of IDH1 mutation is not clear in oligodendroglial tumors that are homogeneously indolent and chemosensitive. In contrast, DAs are heterogeneous tumors including some potentially malignant tumors that can be predicted by examining the IDH1 mutation status.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26235882

DOI: doi.org/10.1016/j.anndiagpath.2015.07.003

Titolo: Coexistent ganglioglioma, focal cortical dysplasia, and hippocampal sclerosis (triple pathology) in chronic epilepsy.

Autori: Prayson RA., Gales JM.

Data di Pubblicazione: 2015-8-4

Abstract: The most commonly identified pathologies in patients with medically intractable epilepsy include focal cortical dysplasia, hippocampal sclerosis, tumors, and remote ischemic damage. Surgery has proven to be an effective therapeutic modality in most of such patients. The coexistence of multiple pathologies in resected tissues is well documented, particularly ganglioglioma and focal cortical dysplasia. Cases of triple pathology are, however, extraordinarily unusual. We report 2 cases of triple pathology including hippocampal sclerosis, ganglioglioma, and focal cortical dysplasia. Cases of patho

logically confirmed hippocampal sclerosis diagnosed between January 2000 to December 2012 (n= 349) were reviewed, and only 2 cases (0.6%) with triple pathology were identified. The histopathologic and clinical features of these 2 cases are reviewed. The patients included a 6-year-old girl and 10-year-old boy. The former patient presented with a 4-year history of epilepsy and oppositional defiant disorder. Imaging identified a lesion in the left parahippocampal gyrus and posterior hippocampus. The latter patient presented with an 8-year history of epilepsy, attention deficient hyperactivity disease, and a pervasive developmental disorder. Imaging identified a lesion in the left posterior temporal and occipital region. Resected tissues in both patients showed a ganglioglioma (World Health Organization grade I) with accompanying focal cortical dysplasia and hippocampal sclerosis. Both patients were seizure free on antiepileptic medication at last follow-up at 20 and 38 months, respectively. The prevalence of triple pathology including hippocampal sclerosis is low (<1% in the current study). Surgical intervention for triple pathology cases anecdotally appears effective in achieving seizure control.  
Journal Title: Annals of diagnostic pathology

PUBMED ID: 26235348

DOI: doi.org/10.1002/ijc.29711

Titolo: Single agent carboplatin for pediatric low-grade glioma: A retrospective analysis shows equivalent efficacy to multiagent chemotherapy.

Autori: Dodgshun AJ., Maixner WJ., Heath JA., Sullivan MJ., Hansford JR.

Data di Pubblicazione: 2015-8-4

Abstract: Pediatric low-grade gliomas (LGG) that are unresectable often require adjuvant chemotherapy such as carboplatin/vincristine. Small Phase II studies have suggested equivalent efficacy of single agent 4-weekly carboplatin. A single-institution retrospective review captured all patients aged 0 to 18 years diagnosed with LGG between 1996 and 2013 and treated with carboplatin monotherapy. The response and survival according to tumor site was compared to published results for multiagent chemotherapy. Of 268 children diagnosed with LGG diagnosed in this period, 117 received chemotherapy and 104 children received single agent carboplatin as first line chemotherapy. All patients received carboplatin at 560 mg/m<sup>2</sup>, four-weekly for a median of 12 courses. The mean age at diagnosis was 5.8 years (range 3m-16y) and 32% had neurofibromatosis type 1. With a mean followup of 54 months, 86% of patients achieved stabilisation or better (SD/PR/CR). 3-year progression free survival (PFS) 66% (95% CI 57-76%), and 5-year PFS was 51% (95% CI 41-63%). 5-year overall survival was 97%. Multivariate analysis showed poorer PFS for those with chiasmatic/hypothalamic tumors. In this retrospective analysis single agent carboplatin shows comparable efficacy to historical multiagent chemotherapy for the treatment of patients with unresectable LGG. Equivalent outcomes are achieved with less chemotherapy, reduced side effects and fewer hospital visits. Further research is required to establish the place of this simplified regimen in the up-front treatment of unresectable LGG.

Journal Title: International journal of cancer

PUBMED ID: 26231569

DOI: doi.org/10.1007/s00381-015-2848-6

Titolo: Cavernous angioma after chemotherapy for desmoplastic/nodular medulloblastoma associated with anhidrotic ectodermal dysplasia.

Autori: Yamasaki F., Takayasu T., Nosaka R., Kawaguchi H., Sugiyama K., Kobayashi M., Kurisu K.

Data di Pubblicazione: 2015-8-2

Abstract: To our knowledge, this is the first report of AED-associated DNMB and CVA.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 26230475

DOI: doi.org/10.3171/2015.1.JNS141577

Titolo: Downregulation of serum microRNA-205 as a potential diagnostic and prognostic biomarker for human glioma.

Autori: Yue X., Lan F., Hu M., Pan Q., Wang Q., Wang J.

Data di Pubblicazione: 2015-8-1

Abstract: OBJECT Circulating microRNAs (miRNAs) are a new class of highly promising cancer biomarkers. Malignant glioma is one of the most devastating and lethal forms of intrinsic CNS tumor. Here, the authors evaluated serum miRNA 205 (miR-205) levels in patients with glioma. METHODS Sixty-four patients in whom glioma was diagnosed and 45 healthy controls were recruited between October 2011 and March 2012 and randomly assigned to the screening cohort or the validation cohort. Cohorts of patients with other brain tumors, including meningioma (n = 8), primary diffuse large B-cell lymphoma of the CNS (n = 6), and pituitary adenoma (n = 5), were investigated and compared. miR-205 extraction from serum was detected by real-time quantitative reverse-transcription polymerase chain reaction. The Kaplan-Meier method was applied to perform survival analysis, the risk factors were analyzed by using a Cox regression model, and the receiver operating characteristic working curve was used to analyze the value of miR-205 in the prognostic evaluation of the patients. RESULTS The authors first demonstrated that serum miR-205 expression was significantly lower in patients with glioma than in healthy controls ( $p < 0.001$ ). It is important to note that serum miR-205 expression demonstrated a stepwise decrease with ascending pathological grades. The serum miR-205 biomarker had high sensitivity, specificity, and accuracy in patients with glioma. Serum levels of miR-205 were identified as an individual diagnostic marker and were significantly lower in the glioma cohort than in the other brain tumor cohorts. Serum miR-205 levels were significantly increased in postoperative samples over those in the preoperative samples and were reduced again during glioblastoma recurrences. Statistical analysis revealed a significant correlation between low serum miR-205 expression and both ascending pathological grades ( $p = 0.002$ ) and low Karnofsky Performance Scale scores ( $p = 0.01$ ). Patients with glioma at an advanced pathological grade (Grade III or IV) and a higher miR-205 serum level showed longer overall survival than those with a lower miR-205 serum concentration ( $p < 0.01$ ). Furthermore, Cox regression analysis revealed that miR-205 serum levels were independently associated with overall survival. CONCLUSIONS These data indicate that serum miR-205 expression is a novel and valuable biomarker for the diagnosis of glioma and a prognostic factor for those with a tumor at an advanced pathological grade. Journal Title: Journal of neurosurgery

PUBMED ID: 26227256

DOI: doi.org/10.5414/NP300864

Titolo: Well-differentiated and anaplastic astroblastoma in the same patient: a case report and review of the literature.

Autori: Samkari A., Hmoud M., Al-Mehdar A., Abdullah S.

Data di Pubblicazione: 2015-8-1

Abstract: Astroblastoma is a rare brain tumor occurring in children and adults, rarely in the elderly. It constitutes up to 3% of all brain tumors. We report a case of a 14-year-old girl who presented with recurrent seizures and minimal right hemiparesis. Magnetic resonance imaging (MRI) revealed a left fronto-parietal brain tumor. It was managed with subtotal resection in a local hospital. Subsequently, she was referred to Princess Nora Oncology Center for further characterization and management. Pathology slide revision revealed well-differentiated astroblastoma. Upon follow up, the patient had multiple recurrences of the same tumor and emergence of a new lesion at the area of Sylvian fissure. Excision of the emerging tumor revealed anaplastic astroblastoma.

lastoma. Astroblastoma is a glial tumor that predominantly affects females. Its clinical progression is unpredictable, with high recurrence rate. Surgical intervention is considered the mainstay of treatment, while radiotherapy and chemotherapy effectiveness is debatable. To our knowledge, this is the first reported case of well-differentiated and anaplastic astroblastoma as two separate neoplastic lesions in the same patient with its clinical, radiological, and pathological features.

Journal Title: Clinical neuropathology

PUBMED ID: 26207600

DOI: doi.org/10.3171/2015.1.JNS142349

Titolo: Magnetic resonance susceptibility weighted imaging in neurosurgery: current applications and future perspectives.

Autori: Di Ieva A., Lam T., Alcaide-Leon P., Bharatha A., Montanera W., Cusimano MD.

Data di Pubblicazione: 2015-7-25

Abstract: Susceptibility weighted imaging (SWI) is a relatively new imaging technique. Its high sensitivity to hemorrhagic components and ability to depict microvasculature by means of susceptibility effects within the veins allow for the accurate detection, grading, and monitoring of brain tumors. This imaging modality can also detect changes in blood flow to monitor stroke recovery and reveal specific subtypes of vascular malformations. In addition, small punctate lesions can be demonstrated with SWI, suggesting diffuse axonal injury, and the location of these lesions can help predict neurological outcome in patients. This imaging technique is also beneficial for applications in functional neurosurgery given its ability to clearly depict and differentiate deep midbrain nuclei and close submillimeter veins, both of which are necessary for presurgical planning of deep brain stimulation. By exploiting the magnetic susceptibilities of substances within the body, such as deoxyhemoglobin, calcium, and iron, SWI can clearly visualize the vasculature and hemorrhagic components even without the use of contrast agents. The high sensitivity of SWI relative to other imaging techniques in showing tumor vasculature and microhemorrhages suggests that it is an effective imaging modality that provides additional information not shown using conventional MRI. Despite SWI's clinical advantages, its implementation in MRI protocols is still far from consistent in clinical usage. To develop a deeper appreciation for SWI, the authors here review the clinical applications in 4 major fields of neurosurgery: neurooncology, vascular neurosurgery, neurotraumatology, and functional neurosurgery. Finally, they address the limitations of and future perspectives on SWI in neurosurgery.

Journal Title: Journal of neurosurgery

PUBMED ID: 26191506

DOI: doi.org/10.3389/fonc.2015.00148

Titolo: Future Clinical Trials in DIPG: Bringing Epigenetics to the Clinic.

Autori: Morales La Madrid A., Hashizume R., Kieran MW.

Data di Pubblicazione: 2015-7-21

Abstract: In spite of major recent advances in diffuse intrinsic pontine glioma (DIPG) molecular characterization, this body of knowledge has not yet translated into better treatments. To date, more than 250 clinical trials evaluating radiotherapy along with conventional cytotoxic chemotherapy as well as newer biologic agents have failed to improve the dismal outcome when compared to palliative radiation alone. The biology of DIPG remained unknown until recently when the neurosurgical expertise along with the recognition by the scientific and clinical community of the importance of tissue sampling at diagnosis; ideally, in the context of a clinical trial and by trained neurosurgical teams to maximize patient safety. These pre-treatment tumor samples, and others coming from tissue obtained post-mortem, have yielded new insight

s into DIPG molecular pathogenesis. We now know that DIPG comprises a heterogeneous disease with variable molecular phenotypes, different from adult high-grade glioma, other non-pontine pediatric high-grade gliomas, and even between pontine gliomas. The discovery of histone H3.3 or H3.1 mutations has been an important step forward in understanding tumor formation, maintenance, and progression. Pharmacologic reversal of DIPG histone demethylation therefore offers an important potential intervention strategy for the treatment of DIPG. To date, clinical trials of newly diagnosed or progressive DIPG with epigenetic (histone) modifiers have been unsuccessful. Whether this failure represents limited activity of the agents used, their CNS penetration, redundant pathways within the tumor, or the possibility that histone mutations are necessary only to initiate DIPGs but not maintain their growth, suggest that a great deal still needs to be elucidated in both the underlying biology of these pathways and the drugs designed to target them. In this review, we will discuss the role of both epigenetic and genetic mutations within DIPG and the development of treatment strategies directed against the unique abnormalities present in this disease.

Journal Title: Frontiers in oncology

PUBMED ID: 26178621

DOI: doi.org/10.1007/s11940-015-0369-y

Titolo: Novel Surgical Approaches to High-Grade Gliomas.

Autori: Rasul FT., Watts C.

Data di Pubblicazione: 2015-7-17

Abstract: Treatment of patients with high-grade glioma (HGG) should begin with thorough evaluation by a specialized multidisciplinary team to determine whether or not the patient is appropriate for surgery, chemotherapy and radiotherapy. Particular attention should be paid to the performance status and neurological function. Surgery is the first step in therapeutic intervention. Patients undergo either biopsy, debulking surgery or maximal resection depending on the anatomical location of the tumour and the patient's clinical condition. Extent of resection has a prognostic value. In patients who are 'fit for surgery', the aim is to remove all contrast-enhancing tumour without causing neurological deficit. If microsurgical resection is not feasible, then a biopsy, either open or stereotactic, should be performed to confirm high-grade glioma diagnosis and to perform molecular genetic analyses (MGMT methylation status, loss of heterozygosity in 1p/19q, IDH1 status) as this has treatment implications. Over the past decade, much glioma research has focused on novel surgical approaches to improve long-term outcomes. The evidence to support the benefit of maximizing extent of resection is growing. Advances in neurosurgical techniques allow safer, more aggressive surgery to maximize tumour resection whilst minimizing neurological deficit. Surgical adjuncts including advanced neuronavigation, intraoperative magnetic resonance imaging, high-frequency ultrasonography, fluorescence-guided microsurgery using intraoperative fluorescence, functional mapping of motor and language pathways, and locally delivered therapies are extending the armamentarium of the neurosurgeon to provide patients with the best outcome. Operating on elderly patients and those with recurrent disease, although controversial, is becoming more common due to emerging neurosurgical approaches. Here, we discuss the emerging surgical techniques and comment on the future of HGG surgery.

Journal Title: Current treatment options in neurology

PUBMED ID: 26175405

DOI: Mancante

Titolo: One size should not fit all: advancing toward personalized glioblastoma therapy.

Autori: Reardon DA., Ligon KL., Chiocca EA., Wen PY.

Data di Pubblicazione: 2015-7-16

**Abstract:** Over the past few years, understanding the genetic abnormalities associated with glioblastoma, the most common malignant primary tumor of the central nervous system, has increased dramatically. Mutation types and frequencies have been comprehensively assessed, glioblastoma subclasses have been defined based on gene expression and methylation analyses, and novel mutations implicated in gliomagenesis have been identified. Nonetheless, a critical disconnect exists between achieved scientific advances and failure to improve patient outcome. Currently, standard therapy incorporating surgery, cranial irradiation, and temozolomide chemotherapy is uniformly applied for all patients. With this approach, median survival remains unacceptably poor including fewer than 10% of patients surviving 5 years after diagnosis. Salvage therapies are ineffective with PFS-6 rates under 10% for non-bevacizumab regimens and 40% for bevacizumab. Furthermore, all patients ultimately progress on bevacizumab, and then typically die from rapidly progressive tumor. Innovative treatment strategies directed to distinct patient subsets defined by specific genetic and gene expression analyses represent an attractive therapeutic paradigm shift for this highly challenging complex tumor, offering promise to ultimately improve outcome.

**Journal Title:** Discovery medicine

PUBMED ID: 26169613

DOI: doi.org/10.1200/JCO.2014.60.1591

**Titolo:** Vismodegib Exerts Targeted Efficacy Against Recurrent Sonic Hedgehog-Subgroup Medulloblastoma: Results From Phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032.

**Autori:** Robinson GW., Orr BA., Wu G., Gururangan S., Lin T., Qaddoumi I., Packer RJ., Goldman S., Prados MD., Desjardins A., Chintagumpala M., Takebe N., Kaste SC., Rusch M., Allen SJ., Onar-Thomas A., Stewart CF., Fouladi M., Boyett JM., Gilbertson RJ., Curran T., Ellison DW., Gajjar A.

**Data di Pubblicazione:** 2015-7-15

**Abstract:** Vismodegib exhibits activity against adult recurrent SHH-MB but not against recurrent non-SHH-MB. Inadequate accrual of pediatric patients precluded conclusions in this population. Molecular analyses support the hypothesis that SMO inhibitor activity depends on the genomic aberrations within the tumor. Such inhibitors should be advanced in SHH-MB studies; however, molecular and genomic work remains imperative to identify target populations that will truly benefit.

**Journal Title:** Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 26162036

DOI: doi.org/10.3171/2014.12.JNS141851

**Titolo:** Acute progression of untreated incidental WHO Grade II glioma to glioblastoma in an asymptomatic patient.

**Autori:** Cochereau J., Herbet G., Rigau V., Duffau H.

**Data di Pubblicazione:** 2015-7-11

**Abstract:** WHO Grade II glioma (low-grade glioma [LGG]) is increasingly diagnosed as an incidental finding in patients undergoing MRI for many conditions. Recent data have demonstrated that such incidental LGGs are progressive tumors that undergo clinical transformation and ultimately become malignant. Although asymptomatic LGG seems to represent an earlier step in the natural course of a glioma than the symptomatic LGG, it is nonetheless impossible to predict at the individual level when the tumor will become malignant. The authors report the case of a 43-year-old woman with a right operculo-insular LGG that was incidentally diagnosed because of headaches. No treatment was proposed, and repeated MRI scans were performed for 6 years in another institution. Due to a slow but continuous growth of the lesion, the patient was finally referred to our center to undergo surgery. Interestingly, objective cal



ulation of the velocity of the tumor's diametric expansion demonstrated a sudden acceleration of the growth rate within the 5 months preceding surgery, with the development of contrast enhancement. Remarkably, the patient was still asymptomatic. An awake resection was performed with intraoperative electrical mapping. There was no functional worsening following surgery, as assessed on postoperative neuropsychological examination. Removal of 92% of signal abnormality on FLAIR MRI was achieved, with complete resection of the area of contrast enhancement. Neuropathological examination revealed a glioblastoma, and the patient was subsequently treated with concomitant radiotherapy and chemotherapy. Although a "wait and see" attitude has been advocated by some authors with respect to incidental LGG, our original case demonstrates that acute transformation to glioblastoma may nonetheless occur, even before the onset of any symptoms. Therefore, because the lack of symptoms does not protect from malignant transformation, we propose consideration of earlier resection in a more systematic manner in cases of incidental LGG.

Journal Title: Journal of neurosurgery

PUBMED ID: 26155413

DOI: doi.org/10.1080/2162402X.2015.1008339

Titolo: Are BiTEs the "missing link" in cancer therapy?

Autori: Suryadevara CM., Gedeon PC., Sanchez-Perez L., Verla T., Alvarez-Breckenridge C., Choi BD., Fecci PE., Sampson JH.

Data di Pubblicazione: 2015-7-9

Abstract: Conventional treatment for cancer routinely includes surgical resection and some combination of chemotherapy and radiation. These approaches are frequently accompanied by unintended and highly toxic collateral damage to healthy tissues, which are offset by only marginal prognostic improvements in patients with advanced cancers. This unfortunate balance has driven the development of novel therapies that aim to target tumors both safely and efficiently. Over the past decade, mounting evidence has supported the therapeutic utility of T-cell-centered cancer immunotherapy, which, in its various iterations, has been shown capable of eliciting highly precise and robust anti-tumor responses both in animal models and human trials. The identification of tumor-specific targets has further fueled a growing interest in T-cell therapies given their potential to circumvent the non-specific nature of traditional treatments. Of the several strategies geared toward achieving T-cell recognition of tumor, bispecific antibodies (bsAbs) represent a novel class of biologics that have garnered enthusiasm in recent years due to their versatility, specificity, safety, cost, and ease of production. Bispecific T-cell Engagers (BiTEs) are a subclass of bsAbs that are specific for CD3 on one arm and a tumor antigen on the second. As such, BiTEs function by recruiting and activating polyclonal populations of T-cells at tumor sites, and do so without the need for co-stimulation or conventional MHC recognition. Blinatumomab, a well-characterized BiTE, has emerged as a promising recombinant bscCD19×CD3 construct that has demonstrated remarkable antitumor activity in patients with B-cell malignancies. This clinical success has resulted in the rapid extension of BiTE technology against a greater repertoire of tumor antigens and the recent US Food and Drug Administration's (FDA) accelerated approval of blinatumomab for the treatment of a rare form of acute lymphoblastic leukemia (ALL). In this review, we dissect the role of T-cell therapeutics in the new era of cancer immunotherapy, appraise the value of CAR T-cells in the context of solid tumors, and discuss why the BiTE platform may rescue several of the apparent deficits and shortcomings of competing immunotherapies to support its widespread clinical application.

Journal Title: Oncoimmunology

PUBMED ID: 26143265

DOI: doi.org/10.1007/s11864-015-0353-5

Titolo: An Evidence-Based Review of Alternating Electric Fields Therapy for Malignant Gliomas.

Autori: Wong ET., Lok E., Swanson KD.

Data di Pubblicazione: 2015-7-6

Abstract: Glioblastoma is a deadly disease and even aggressive neurosurgical resection followed by radiation and chemotherapy only extends patient survival to a median of 1.5 years. The challenge in treating this type of tumor stems from the rapid proliferation of the malignant glioma cells, the diffuse infiltrative nature of the disease, multiple activated signal transduction pathways within the tumor, development of resistant clones during treatment, the blood brain barrier that limits the delivery of drugs into the central nervous system, and the sensitivity of the brain to treatment effect. Therefore, new therapies that possess a unique mechanism of action are needed to treat this tumor. Recently, alternating electric fields, also known as tumor treating fields (TTFields), have been developed for the treatment of glioblastoma. TTFields use electromagnetic energy at an intermediate frequency of 200 kHz as a locoregional intervention and act to disrupt tumor cells as they undergo mitosis. In a phase III clinical trial for recurrent glioblastoma, TTFields were shown to have equivalent efficacy when compared to conventional chemotherapies, while lacking the typical side effects associated with chemotherapies. Furthermore, an interim analysis of a recent clinical trial in the upfront setting demonstrated superiority to standard of care cytotoxic chemotherapy, most likely because the subjects' tumors were at an earlier stage of clonal evolution, possessed less tumor-induced immunosuppression, or both. Therefore, it is likely that the efficacy of TTFields can be increased by combining it with other anti-cancer treatment modalities.

Journal Title: Current treatment options in oncology

PUBMED ID: 26142814

DOI: doi.org/10.1016/j.wneu.2015.06.058

Titolo: Synchronous Subarachnoid Aneurysmal Hemorrhage and Medulloblastoma in a 6-Year-Old Girl.

Autori: Foley RW., Nodoro S., Crimmins D., Caird J.

Data di Pubblicazione: 2015-7-6

Abstract: Intraoperative hemorrhage in MB is a very rare occurrence. We describe the first case of hemorrhage in MB secondary to an intracranial aneurysm. MB has a predisposition to bleed spontaneously that can have catastrophic repercussions. Sudden clinical deterioration after insertion of external ventricular drainage should be susceptible of intracerebral hemorrhage. In cases of uncertain etiology, investigation of SAH with cerebral angiography is recommended.

Journal Title: World neurosurgery

PUBMED ID: 26114990

DOI: doi.org/10.3171/2015.5.PEDS14638

Titolo: Cervicomedullary tumors in children.

Autori: McAbee JH., Modica J., Thompson CJ., Broniscer A., Orr B., Choudhri AF., Boop FA., Klimo P.

Data di Pubblicazione: 2015-6-27

Abstract: Children with CMTs typically have low-grade neoplasms and consequently long-term survival, but high risk of recurrence. Therapy should be directed at achieving local tumor control while preserving and even restoring neurological function.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 26070556

DOI: doi.org/10.1007/s11060-015-1844-8

Titolo: Re-irradiation or re-operation followed by dendritic cell vaccination? Comparison of two different salvage strategies for relapsed high-grade gliomas by means of a new prognostic model.

Autori: Müller K., Henke G., Pietschmann S., van Gool S., De Vleeschouwer S., von Bueren AO., Compter I., Friedrich C., Matuschek C., Klautke G., Kortmann RD., Hunsberger T., Baumert BG.

Data di Pubblicazione: 2015-6-14

Abstract: We aimed to compare two different salvage treatment strategies for relapsed high-grade glioma (HGG) patients by means of a new prognostic model. A simplified version of the so-called HGG-Immuno RPA model estimates the prognosis of relapsed HGG patients and distinguishes three different prognostic classes (I = good, II = intermediate, III = poor). The model has been constructed with a cohort of 117 patients whose salvage treatment consisted of re-operation followed by dendritic cell vaccination (ReOP + DCV). However, using only the predictors histology, age and performance status, the simplified HGG-Immuno RPA model is basically independent from treatment. In the present study we applied the simplified model to the cohort used to construct the original HGG-Immuno RPA model and another cohort of 165 patients who underwent re-irradiation (ReRT) at relapse. Then, we compared the outcomes achieved by the two different salvage treatments in each prognostic class. The model predicted good, intermediate and poor prognosis for 11, 31 and 75 patients of the ReOP + DCV cohort and for 20, 39 and 106 patients of the ReRT cohort, respectively. Neither of the two strategies was superior to the other. In the groups with good, intermediate and poor prognosis 12-months survival rates were 73, 59 and 25 % after ReOP + DCV and 72, 36 and 23 % after ReRT, respectively. Being easy to handle and independent from treatment, the aforementioned model is useful for therapeutic decisions. ReRT and ReOP + DCV seem to be equally effective. The choice of salvage treatment should be based on the expected side effects.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26034641

DOI: doi.org/10.1093/nop/npu031

Titolo: Large volume re-irradiation with bevacizumab is a feasible salvage option for patients with refractory high-grade glioma.

Autori: Back M., Gzell CE., Kastelan M., Guo L., Wheeler HR.

Data di Pubblicazione: 2015-6-3

Abstract: ReRT combined with BEV is a feasible salvage treatment option for diffuse refractory HGG.

Journal Title: Neuro-oncology practice

PUBMED ID: 26029663

DOI: doi.org/10.3389/fonc.2015.00106

Titolo: Salvage Fractionated Stereotactic Radiotherapy with or without Chemotherapy and Immunotherapy for Recurrent Glioblastoma Multiforme: A Single Institution Experience.

Autori: Hasan S., Chen E., Lanciano R., Yang J., Hanlon A., Lamond J., Arriguo S., Ding W., Mikhail M., Ghaneie A., Brady L.

Data di Pubblicazione: 2015-6-2

Abstract: Radiation Therapy Oncology Group (RTOG) 1205 will establish the role of re-irradiation for recurrent GBM, however our study suggests that CyberKnife with chemotherapy can be safely delivered, and is most effective in patients with smaller frontal lobe tumors, good performance status, or long interval from diagnosis.

Journal Title: Frontiers in oncology

PUBMED ID: 26026859

DOI: doi.org/10.1007/s11060-015-1808-z

Titolo: Prognostic implication of progression pattern after anti-VEGF bevacizumab treatment for recurrent malignant gliomas.

Autori: Kim BS., Kim SK., Choi SH., Lee SH., Seol HJ., Nam DH., Lee JI., Park CK., Kong DS.

Data di Pubblicazione: 2015-6-1

Abstract: Malignant glioma treated with anti-vascular endothelial growth factor (VEGF) bevacizumab show progression patterns that vary with different mechanisms of resistance. We evaluated the clinico-radiological data of 71 patients with progressive malignant glioma treated with bevacizumab to determine the prognostic value of the differential outcome of each progression pattern. Progression patterns were categorized as three types based on the initial response to bevacizumab and serious changes of MR images i.e., non-enhancing infiltration, flare-up of contrast enhancement (CE) and primary non-responder progression. We analyzed the clinical outcome in each type of progression using Kaplan-Meier survival analysis. Analysis of progression patterns showed that incidence of non-enhancing infiltration progression (28.1 %) was less common than flare-up of CE or primary non-responder pattern. The time from initiation of bevacizumab to development of non-enhancing infiltration or flare-up of CE progression was longer than for progression in primary non-responders. There was no significant difference of overall survival, progression-free survival from start of bevacizumab therapy, survival after bevacizumab failure between non-enhancing infiltration and flare-up of CE patterns. However, in the non-enhancing infiltration pattern, early appearance of enhancement was observed after bevacizumab was discontinued, resulting in poor survival, as compared to flare-up of CE pattern ( $P = 0.01$ ). Although the appearance of non-enhancing infiltration after bevacizumab does not imply a worse prognosis, discontinuation of therapy can aggravate the clinical course.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26025933

DOI: doi.org/10.1634/theoncologist.2015-0135

Titolo: Phase II Trial of Upfront Bevacizumab, Irinotecan, and Temozolomide for Unresectable Glioblastoma.

Autori: Peters KB., Lou E., Desjardins A., Reardon DA., Lipp ES., Miller E., Herndon JE., McSherry F., Friedman HS., Vredenburgh JJ.

Data di Pubblicazione: 2015-5-31

Abstract: Upfront treatment with BV, TMZ, and CPT-11 is tolerable and can lead to radiographic response in unresectable and/or subtotally resected GBM.

Journal Title: The oncologist

PUBMED ID: 26024653

DOI: doi.org/10.1007/s11060-015-1825-y

Titolo: Re-resection for recurrent high-grade glioma in the setting of re-irradiation: more is not always better.

Autori: Palmer JD., Siglin J., Yamoah K., Dan T., Champ CE., Bar-Ad V., Werner-Wasik M., Evans JJ., Kim L., Glass J., Farrell C., Andrews DW., Shi W.

Data di Pubblicazione: 2015-5-31

Abstract: The optimal treatment for patients with recurrent high grade glioma (HGG) remains controversial. Available therapies include surgery, re-irradiation, alternating electric fields or systemic therapy. Here we investigate whether re-resection will improve survival in patients receiving repeat radiotherapy for tumor recurrence. 231 consecutive patients with recurrent HGG treated with re-irradiation between 1994 and 2012 were analyzed. 105 patients underwent re-resection. Re-irradiation was delivered using daily fractions of 3.5 Gy to a median total dose of 35 Gy. Survival was then analyzed comparing patients with and without re-resection. Overall survival (OS) and survival from the first recurrence are reported. Univariate and cox-proportional ha

zard modeling was performed in a step-wise multivariate analysis using known prognostic factors. The median follow-up time from initial diagnosis was 25.7 months. The median OS from initial diagnosis of the entire group was 22.5 months. There was no significant difference in median overall survival between patients who received re-resection versus no re-resection, 23 versus 21.9 months respectively ( $p = 0.6$ ). Additionally, there was no difference in median survival from the time of first recurrence 10.5 months without re-resection versus 11.1 months with re-resection ( $p = 0.09$ ). After adjusting for known prognostic variables, only age remained significant. Re-irradiation is an effective salvage therapy for patients with localized, progressive high grade glioma, achieving a median survival of 10-11 months from re-irradiation. Our data reveals no significant improvement in survival with the addition of re-resection to re-irradiated patients with HGG.

Journal Title: Journal of neuro-oncology

PUBMED ID: 26012492

DOI: doi.org/10.1016/j.neuroscience.2015.05.037

Titolo: Imaging of autoimmune encephalitis--Relevance for clinical practice and hippocampal function.

Autori: Heine J., Prüss H., Bartsch T., Ploner CJ., Paul F., Finke C.

Data di Pubblicazione: 2015-5-28

Abstract: The field of autoimmune encephalitides associated with antibodies targeting cell-surface antigens is rapidly expanding and new antibodies are discovered frequently. Typical clinical presentations include cognitive deficits, psychiatric symptoms, movement disorders and seizures and the majority of patients respond well to immunotherapy. Pathophysiological mechanisms and clinical features are increasingly recognized and indicate hippocampal dysfunction in most of these syndromes. Here, we review the neuroimaging characteristics of autoimmune encephalitides, including N-methyl-d-aspartate (NMDA) receptor, leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2) encephalitis as well as more recently discovered and less frequent forms such as dipeptidyl-peptidase-like protein 6 (DPPX) or glycine receptor encephalitis. We summarize findings of routine magnetic resonance imaging (MRI) investigations as well as (18)F-fluoro-2-deoxy-d-glucose (FDG)-positron emission tomography (PET) and single photon emission tomography (SPECT) imaging and relate these observations to clinical features and disease outcome. We furthermore review results of advanced imaging analyses such as diffusion tensor imaging, volumetric analyses and resting-state functional MRI. Finally, we discuss contributions of these neuroimaging observations to the understanding of the pathophysiology of autoimmune encephalitides.

Journal Title: Neuroscience

PUBMED ID: 25977905

DOI: doi.org/10.14791/btrt.2015.3.1.34

Titolo: Primary diffuse leptomeningeal gliosarcomatosis.

Autori: Moon JH., Kim SH., Kim EH., Kang SG., Chang JH.

Data di Pubblicazione: 2015-5-16

Abstract: Primary diffuse leptomeningeal gliomatosis (PDLG) is a rare condition with a fatal outcome, characterized by diffuse infiltration of the leptomeninges by neoplastic glial cells without evidence of primary tumor in the brain or spinal cord parenchyma. In particular, PDLG histologically diagnosed as gliosarcoma is extremely rare, with only 2 cases reported to date. We report a case of primary diffuse leptomeningeal gliosarcomatosis. A 68-year-old man presented with fever, chills, headache, and a brief episode of mental deterioration. Initial T1-weighted post-contrast brain magnetic resonance imaging (MRI) showed diffuse leptomeningeal enhancement without a definite intraparenchymal lesion. Based on clinical and imaging findings, antiviral treatment was initiated. Despite the treatment, the patient's neurologic symptoms

oms and mental status progressively deteriorated and follow-up MRI showed rapid progression of the disease. A meningeal biopsy revealed gliosarcoma and was conclusive for the diagnosis of primary diffuse leptomeningeal gliosarcomatosis. We suggest the inclusion of PDLG in the potential differential diagnosis of patients who present with nonspecific neurologic symptoms in the presence of leptomeningeal involvement on MRI.

Journal Title: Brain tumor research and treatment

PUBMED ID: 25949228

DOI: doi.org/10.1016/j.rpor.2015.01.004

Titolo: Fractionated stereotactic radiotherapy plus bevacizumab after response to bevacizumab plus irinotecan as a rescue treatment for high-grade gliomas.

Autori: Conde-Moreno AJ., García-Gómez R., Albert-Antequera M., Almendros-Blanco P., De Las Peñas-Bataller R., González-Vidal V., López-Torrecilla JL., Ferrer-Albiach C.

Data di Pubblicazione: 2015-5-8

Abstract: The combination of BVZ+FSRT as a second-line HGG relapse rescue treatment is well-tolerated and seems to offer promising results. We believe that multi-centre prospective studies are needed to determine the long-term efficacy and toxicity of this therapeutic approach.

Journal Title: Reports of practical oncology and radiotherapy : journal of Greater Poland Cancer Center in Poznan and Polish Society of Radiation Oncology

PUBMED ID: 25907866

DOI: doi.org/10.1016/j.humpath.2015.01.023

Titolo: MicroRNA-144 suppresses tumorigenesis and tumor progression of astrocytoma by targeting EZH2.

Autori: Lin L., Zheng Y., Tu Y., Wang Z., Liu H., Lu X., Xu L., Yuan J.

Data di Pubblicazione: 2015-4-25

Abstract: Our previous study demonstrated that enhancer of zeste homolog 2 (EZH2) overexpression may be associated with aggressive tumor progression and poor prognosis in human astrocytoma. The aim of this study was to investigate the underlying mechanisms of EZH2 on astrocytoma tumorigenesis. An online program miRWalk (<http://www.umm.uni-heidelberg.de/apps/zmf/mirwalk/>) was used to predict possible microRNAs (miRNAs) that might target EZH2 messenger RNA (mRNA). Then the functions of the miRNA-EZH2 mRNA axis in astrocytoma cell proliferation, invasion, and migration were also assessed. We further evaluated the clinical value of the miRNA-EZH2 mRNA axis in astrocytomas. As a result, we identified EZH2 as a target gene of miR-144. In addition, forced expression of miR-144 suppressed astrocytoma cell proliferation, invasion, and migration by down-regulating EZH2. Moreover, miR-144 down-regulation and EZH2 mRNA up-regulation were both significantly associated with advanced World Health Organization grades and low Karnofsky performance status score of astrocytoma patients. Importantly, survival analysis identified the combined expression of miR-144 and EZH2 (miR-144/EZH2) as an independent prognostic factor for overall survival in astrocytoma patients. In conclusion, miR-144 may function as a tumor suppressor by regulating EZH2 expression, and miR-144/EZH2 expression may be a highly sensitive marker for the prognosis in astrocytoma patients.

Journal Title: Human pathology

PUBMED ID: 25894594

DOI: doi.org/10.1007/s11060-015-1774-5

Titolo: Characterization of pseudoprogression in patients with glioblastoma: is histology the gold standard?

Autori: Melguizo-Gavilanes I., Bruner JM., Guha-Thakurta N., Hess KR., Puduvalli VK.

Data di Pubblicazione: 2015-4-21

Abstract: Pseudoprogression (psPD) refers to an increase in size or appearance of new areas of MRI contrast enhancement soon after completing chemoradiation, timely diagnosis of which has been a challenge. Given that tissue sampling of the MRI changes would be expected to accurately distinguish psPD from true progression when MRI changes are first seen, we examined the utility of surgery in diagnosing psPD and influencing patient outcome. We retrospectively reviewed data from adults with GBM who had MRI changes suggestive of progression within 3 months of chemoRT; of these, 34 underwent surgical resection. Three subsets-tumor, psPD or mixed-were identified based on histology and immunohistochemistry in the surgical group and by imaging characteristics in the nonsurgical group. A cohort of patients with stable disease post-chemoRT served as control. PFS and OS were determined using the Kaplan-Meier method and log rank analysis. Concordance for psPD between radiological interpretation and subsequent histological diagnosis was seen in only 32% of cases (11/34) 95%CI 19-49%. A large proportion of patients had a histologically "mixed" pattern with tumor and treatment effect. No significant differences in PFS or OS were seen among the three subtypes. Surgical sampling and histologic review of MRI changes after chemoRT may not serve as a gold standard to distinguish psPD from true progression in GBM patients. Refinement of the histological criteria, careful intraoperative selection of regions of interest and advanced imaging modalities are needed for early differentiation of psPD from progression to guide clinical management.

Journal Title: Journal of neuro-oncology

PUBMED ID: 25823657

DOI: doi.org/10.18632/oncotarget.3229

Titolo: HOTAIR is a therapeutic target in glioblastoma.

Autori: Zhou X., Ren Y., Zhang J., Zhang C., Zhang K., Han L., Kong L., Wei J., Chen L., Yang J., Wang Q., Zhang J., Yang Y., Jiang T., Li M., Kang C.

Data di Pubblicazione: 2015-4-1

Abstract: HOTAIR is a negative prognostic factor and is overexpressed in multiple human cancers including glioblastoma multiforme (GBM). Survival analysis of Chinese Glioma Genome Atlas (CGGA) patient data indicated that high HOTAIR expression was associated with poor outcome in GBM patients. NLK (Nemo-like kinase), a negative regulator of the  $\beta$ -catenin pathway, was negatively correlated with HOTAIR expression. When the  $\beta$ -catenin pathway was inhibited, GBM cells became susceptible to cell cycle arrest and inhibition of invasion. Introduction of the HOTAIR 5' domain in human glioma-derived astrocytoma induced  $\beta$ -catenin. An intracranial animal model was used to confirm that HOTAIR depletion inhibited GBM cell migration/invasion. In the orthotopic model, HOTAIR was required for GBM formation in vivo. In summary, HOTAIR is a potential therapeutic target in GBM.

Journal Title: Oncotarget

PUBMED ID: 25797780

DOI: doi.org/10.2176/nmc.ra.2014-0348

Titolo: Trends and outcomes in the treatment of gliomas based on data during 2001-2004 from the Brain Tumor Registry of Japan.

Autori: Narita Y., Shibui S., Shibui S.

Data di Pubblicazione: 2015-3-24

Abstract: The committee of Brain Tumor Registry of Japan (BTRJ) was founded in 1973 and conducts surveys and analyses of incidence, therapeutic methods, and treatment outcomes of primary and metastatic brain tumors with the cooperation of the Japan Neurosurgical Society members. Newly diagnosed 3,000-4,000 primary brain tumors and 600-1,000 brain metastases patients were enrolled

d in each year. This report describes the trends and treatment outcomes of gliomas from BTRJ volume 13, including 13,431 patients with primary brain tumors who newly started treatment from 2001 to 2004. Data from 382 diffuse astrocytomas (DAs), 121 oligodendrogliomas (OLs), 90 oligoastrocytomas (OAs), 513 anaplastic astrocytomas (AAs), 126 anaplastic oligodendrogliomas (AOs), 106 anaplastic oligoastrocytomas (AOAs), and 1,489 glioblastomas (GBMs) were analyzed for overall survival (OS) and progression free survival (PFS) depending on age, symptoms, Karnofsky performance status, location of the tumor, extent of resection (EOR), initial radiotherapy and chemotherapy. The 5-year PFS rates of the patients with DA, OL+OA, AA, AO+AOA, and GBM were 57.0%, 74.6%, 28.7%, 54.0%, and 9.2%, and the 5-year OS rates were 75.0%, 90.0%, 41.1%, 68.2%, and 10.1%, respectively. Higher EOR $\geq$ 75% in DA and OL+OA and that  $\geq$  50% in AA, AO+AOA, and GBM significantly prolonged OS. Complications and cause of death were also reported. BTRJ had been edited for all the patients, researchers, and especially for clinicians at bedside to give useful information about brain tumors and to contribute to the advances in brain tumor treatment. This report revealed various clinical problematic issues pertaining to the diagnosis and treatment of gliomas.

Journal Title: Neurologia medico-chirurgica

PUBMED ID: 25797075

DOI: doi.org/10.1016/j.wneu.2015.03.018

Titolo: Efficacy of Surgery and Further Treatment of Progressive Glioblastoma.

Autori: Woernle CM., Péus D., Hofer S., Rushing EJ., Held U., Bozinov O., Krayenbühl N., Weller M., Regli L.

Data di Pubblicazione: 2015-3-24

Abstract: Surgery of progressive glioblastoma and postoperative treatment at the time of progression is associated with improved OS in some patients. The addition of age may improve survival prediction of the NIH recurrent glioblastoma scale.

Journal Title: World neurosurgery

PUBMED ID: 25773883

DOI: doi.org/10.1016/j.ejmp.2015.02.011

Titolo: Microbeam radiation therapy: Clinical perspectives.

Autori: Grotzer MA., Schültke E., Bräuer-Krisch E., Laissue JA.

Data di Pubblicazione: 2015-3-17

Abstract: Microbeam radiation therapy (MRT), a novel form of spatially fractionated radiotherapy (RT), uses arrays of synchrotron-generated X-ray microbeams (MB). MRT has been identified as a promising treatment concept that might be applied to patients with malignant central nervous system (CNS) tumors for whom, at the current stage of development, no satisfactory therapy is available yet. Preclinical experimental studies have shown that the CNS of healthy rodents and piglets can tolerate much higher radiation doses delivered by spatially separated MBs than those delivered by a single, uninterrupted, macroscopically wide beam. High-dose, high-precision radiotherapies such as MRT with reduced probabilities of normal tissue complications offer prospects of improved therapeutic ratios, as extensively demonstrated by results of experiments published by many international groups in the last two decades. The significance of developing MRT as a new RT approach cannot be understated. Up to 50% of cancer patients receive conventional RT, and any new treatment that provides better tumor control whilst preserving healthy tissue is likely to significantly improve patient outcomes.

Journal Title: Physica medica : PM : an international journal devoted to the applications of physics to medicine and biology : official journal of the Italian Association of Biomedical Physics (AIFB)



PUBMED ID: 25762141

DOI: doi.org/10.1038/nature14320

Titolo: Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients.

Autori: Mitchell DA., Batich KA., Gunn MD., Huang MN., Sanchez-Perez L., Nair SK., Congdon KL., Reap EA., Archer GE., Desjardins A., Friedman AH., Friedman HS., Herndon JE., Coan A., McLendon RE., Reardon DA., Vredenburgh JJ., Bigner DD., Sampson JH.

Data di Pubblicazione: 2015-3-13

Abstract: After stimulation, dendritic cells (DCs) mature and migrate to draining lymph nodes to induce immune responses. As such, autologous DCs generated ex vivo have been pulsed with tumour antigens and injected back into patients as immunotherapy. While DC vaccines have shown limited promise in the treatment of patients with advanced cancers including glioblastoma, the factors dictating DC vaccine efficacy remain poorly understood. Here we show that pre-conditioning the vaccine site with a potent recall antigen such as tetanus/diphtheria (Td) toxoid can significantly improve the lymph node homing and efficacy of tumour-antigen-specific DCs. To assess the effect of vaccine site pre-conditioning in humans, we randomized patients with glioblastoma to pre-conditioning with either mature DCs or Td unilaterally before bilateral vaccination with DCs pulsed with Cytomegalovirus phosphoprotein 65 (pp65) RNA. We and other laboratories have shown that pp65 is expressed in more than 90% of glioblastoma specimens but not in surrounding normal brain, providing an unparalleled opportunity to subvert this viral protein as a tumour-specific target. Patients given Td had enhanced DC migration bilaterally and significantly improved survival. In mice, Td pre-conditioning also enhanced bilateral DC migration and suppressed tumour growth in a manner dependent on the chemokine CCL3. Our clinical studies and corroborating investigations in mice suggest that pre-conditioning with a potent recall antigen may represent a viable strategy to improve anti-tumour immunotherapy.

Journal Title: Nature

PUBMED ID: 25732040

DOI: doi.org/10.1093/annonc/mdv127

Titolo: Glioblastoma adaptation traced through decline of an IDH1 clonal driver and macro-evolution of a double-minute chromosome.

Autori: Favero F., McGranahan N., Salm M., Birkbak NJ., Sanborn JZ., Benz SC., Becq J., Peden JF., Kingsbury Z., Grocock RJ., Humphray S., Bentley D., Spencer-Dene B., Gutteridge A., Brada M., Roger S., Dietrich PY., Forshew T., Gerlinger M., Rowan A., Stamp G., Eklund AC., Szallasi Z., Swanton C.

Data di Pubblicazione: 2015-3-4

Abstract: This case sheds light on the dynamic evolution of a GBM tumour, defining the origins of the lethal sub-clone, the macro-evolutionary genomic events dominating the disease at recurrence and the loss of a clonal driver. Even in the era of rapid WGS analysis, cases such as this illustrate the significant hurdles for precision medicine success.

Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 25702676

DOI: doi.org/10.5301/tj.5000210

Titolo: The added value of bevacizumab concomitantly administered with carboplatin versus carboplatin alone in patients with recurrent glioblastomas.

Autori: Kaloshi G., Diamandi P., Cakani B., Brace G., Rroji A., Petrela M.

Data di Pubblicazione: 2015-2-24

Abstract: The combination of BEV and CBDCA is associated with improved response rates and survival compared with CBDCA alone. These results highlight th

e value of BEV in recurrent GBM. However, the clinical benefit of this interesting approach needs validation in a larger patient cohort.  
Journal Title: Tumori

PUBMED ID: 25702193

DOI: doi.org/10.1007/s11060-015-1745-x

Titolo: Hypofractionated stereotactic radiotherapy in combination with bevacizumab or fotemustine for patients with progressive malignant gliomas.

Autori: Minniti G., Agolli L., Falco T., Scaringi C., Lanzetta G., Caporello P., Osti MF., Esposito V., Enrici RM.

Data di Pubblicazione: 2015-2-23

Abstract: To evaluate the efficacy of hypofractionated stereotactic radiotherapy performed as reirradiation in combination with fotemustine or bevacizumab as salvage treatment in patients with recurrent malignant glioma. Between May 2006 and December 2013, 54 patients with recurrent malignant glioma received hypofractionated stereotactic radiotherapy (HSRT, 25 Gy in 5-Gy fractions) plus either fotemustine or bevacizumab at University of Rome Sapienza, Sant'Andrea Hospital. All patients had Karnofsky performance score (KPS)  $\geq 60$  and were previously treated with standard chemoradiotherapy. Forty-two patients had a GBM and 12 patients had an anaplastic astrocytoma (AA). The median overall survival (OS) time and 12-month OS rates after HSRT was 11 months and 30 % for patients treated with HSRT plus bevacizumab and 8.3 months and 5 % for those treated with HSRT plus fotemustine ( $p = 0.01$ ). Median PFS times were 4 and 6 months for patients treated with HSRT plus fotemustine or bevacizumab, respectively ( $p = 0.01$ ). KPS  $> 70$  ( $p = 0.04$ ), AA histology, and the treatment with bevacizumab were independent favourable prognostic factors for OS. In general, both treatments were well tolerated with relatively low treatment-related toxicity. HSRT combined with bevacizumab or fotemustine may represent a feasible treatment option for patients with progressive malignant gliomas, although most of the tumors recur in a few months. Efficacy of bevacizumab or alkylating agents in combination with different radiation schedules needs to be evaluated in prospective studies.

Journal Title: Journal of neuro-oncology

PUBMED ID: 25688497

DOI: doi.org/10.1700/1778.19268

Titolo: Impact of 11C-methionine positron emission tomography/computed tomography on radiation therapy planning and prognosis in patients with primary brain tumors.

Autori: Schinkelshoek M., Lopci E., Clerici E., Alongi F., Mancosu P., Rodari M., Navarria P., van der Hiel B., Scorsetti M., Chiti A.

Data di Pubblicazione: 2015-2-18

Abstract: Despite the limited study population, our data indicate that MET-PET/CT can have a significant impact on radiation therapy planning in patients with primary brain tumors. Moreover, treatment modification according to PET appears to be a predictor of clinical outcome in this group of patients.

Journal Title: Tumori

PUBMED ID: 25672644

DOI: doi.org/10.1007/s11060-015-1735-z

Titolo: Disseminated oligodendroglial-like leptomeningeal tumors: preliminary diagnostic and therapeutic results for a novel tumor entity [corrected].

Autori: Preuss M., Christiansen H., Merkschlager A., Hirsch FW., Kiess W., Müller W., Kästner S., Henssler A., Pekrun A., Hauch H., Nathrath M., Meixensberger J., Pietsch T., Kuchelmeister K.

Data di Pubblicazione: 2015-2-13

**Abstract:** Pediatric tumors of the central nervous system composed of oligoid tumor cells showing diffuse leptomeningeal spread without a primary mass lesion seem to represent a novel tumor entity. The terms "diffuse leptomeningeal glioneural tumor" or-preferably-"disseminated oligodendroglial-like leptomeningeal tumor of childhood" (DOGLT) were proposed. Four patients were identified with clinico-neuropathologic findings compatible with DOGLT and a mean follow-up time of 54 months was determined. Seven different biopsies obtained from the four patients were histologically evaluated. Clinical course, diagnostic measures, histopathologic and radiologic features and treatment suggestions were recorded, on the basis of which diagnostic and therapeutic algorithm was proposed. Patients with DOGLT presented with hydrocephalus as first symptom, requiring neurosurgical therapy. Open arachnoid biopsy was necessary to confirm diagnosis. The oligoid cells in a desmoplastic or focally myxoid matrix showed OLIG2-, MAP2-, S-100 and rare HuC/HuD protein-immunopositivity. IDH1 (R132H)- and CD99-immunohistochemistry was negative in all patients. None of the evaluable biopsies of three patients showed chromosome 1p/19q deletion, neither as isolated nor combined allelic loss. Chemotherapy according to the SIOP-LGG 2004 standard induction and consolidation protocol resulted in complete response and partial response, respectively, in 50 % of the patients. However, after discontinuation of chemotherapy, two patients experienced tumor progression and one of them succumbed to the disease after 19 months. Radiological criteria as well as preliminary treatment results are presented after observation of four clinical cases. Prognosis and long-term clinical courses remain to be observed.

**Journal Title:** Journal of neuro-oncology

PUBMED ID: 25655102

DOI: doi.org/10.1158/1078-0432.CCR-14-2737

**Titolo:** MGMT Promoter Methylation Is a Strong Prognostic Biomarker for Benefit from Dose-Intensified Temozolomide Rechallenge in Progressive Glioblastoma: The DIRECTOR Trial.

**Autori:** Weller M., Tabatabai G., Kästner B., Felsberg J., Steinbach JP., Wick A., Schnell O., Hau P., Herrlinger U., Sabel MC., Wirsching HG., Ketter R., Bähr O., Platten M., Tonn JC., Schlegel U., Marosi C., Goldbrunner R., Stupp R., Homicsko K., Pichler J., Nikkhah G., Meixensberger J., Vajkoczy P., Kollias S., Hüsing J., Reifenberger G., Wick W., Wick W.

**Data di Pubblicazione:** 2015-2-7

**Abstract:** Temozolomide rechallenge is a treatment option for MGMT promoter-methylated recurrent glioblastoma. Alternative strategies need to be considered for patients with progressive glioblastoma without MGMT promoter methylation.

**Journal Title:** Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 25609769

DOI: doi.org/10.1212/WNL.0000000000001262

**Titolo:** Biological tumor volume in 18FET-PET before radiochemotherapy correlates with survival in GBM.

**Autori:** Suchorska B., Jansen NL., Linn J., Kretzschmar H., Janssen H., Eigenbrod S., Simon M., Pöpperl G., Kreth FW., la Fougere C., Weller M., Tonn JC., Tonn JC.

**Data di Pubblicazione:** 2015-1-23

**Abstract:** BTV(preRCx) and TAC represent important (18)FET-PET-derived imaging biomarkers in GBM. Increasing TACs are associated with prolonged OS. The BTV(preRCx) is a strong prognostic factor for progression-free survival and OS independent of the mode of surgery. Our data furthermore suggest that patients harboring resectable GBM might benefit from maximal PET-guided tumor resection.

Journal Title: Neurology

PUBMED ID: 25601471

DOI: doi.org/10.2174/1566524015666150114115427

Titolo: Targeting the PI3K/AKT/mTOR signaling pathway in medulloblastoma.

Autori: Dimitrova V., Arcaro A.

Data di Pubblicazione: 2015-1-21

Abstract: Medulloblastoma is the most common malignant childhood brain tumor and is associated with a poor outcome. There is an urgent need to develop novel targeted therapeutic approaches for medulloblastoma, which will arise from an enhanced understanding of the disease at the molecular level. Medulloblastoma has been recognized to be a heterogeneous disease, and no recurrent cancer gene mutations have been found, although many of the mutations described so far affect key intracellular signaling pathways, such as sonic hedgehog (SHH) and Wnt/ $\beta$ -catenin. The PI3K/AKT/mTOR (PAM) signaling pathway controls key cellular responses, such as cell growth and proliferation, survival, migration and metabolism. Over the last decades, it has been recognized that this intracellular signaling pathway is frequently activated by genetic and epigenetic alterations in malignant brain tumors, including medulloblastoma. Clinical trials have started to evaluate the safety and efficacy of agents targeting this pathway in malignant brain tumors. Due to the complexity of the PAM signaling pathway, there remain significant difficulties in the development of novel therapeutic approaches. The future challenges in developing effective treatments for cancer patients include the development of predictive biomarkers and combinatorial approaches to effectively target multiple signal transduction pathways. In this review article, we will summarize the current knowledge about the role of PAM signaling in medulloblastoma and discuss the strategies that are currently being evaluated with targeted agents against this pathway.

Journal Title: Current molecular medicine

PUBMED ID: 25599276

DOI: doi.org/10.3171/2014.10.FOCUS14651

Titolo: Proposed therapeutic strategy for adult low-grade glioma based on aggressive tumor resection.

Autori: Nitta M., Muragaki Y., Maruyama T., Ikuta S., Komori T., Maebayashi K., Iseki H., Tamura M., Saito T., Okamoto S., Chernov M., Hayashi M., Okada Y.

Data di Pubblicazione: 2015-1-20

Abstract: OBJECT There is no standard therapeutic strategy for low-grade glioma (LGG). The authors hypothesized that adjuvant therapy might not be necessary for LGG cases in which total radiological resection was achieved. Accordingly, they established a treatment strategy based on the extent of resection (EOR) and the MIB-1 index: patients with a high EOR and low MIB-1 index were observed without postoperative treatment, whereas those with a low EOR and/or high MIB-1 index received radiotherapy (RT) and/or chemotherapy. In the present retrospective study, the authors reviewed clinical data on patients with primarily diagnosed LGGs who had been treated according to the above-mentioned strategy, and they validated the treatment policy. Given their results, they will establish a new treatment strategy for LGGs stratified by EOR, histological subtype, and molecular status. METHODS One hundred fifty-three patients with diagnosed LGG who had undergone resection or biopsy at Tokyo Women's Medical University between January 2000 and August 2010 were analyzed. The patients consisted of 84 men and 69 women, all with ages  $\geq 15$  years. A total of 146 patients underwent surgical removal of the tumor, and 7 patients underwent biopsy. RESULTS Postoperative RT and nitrosourea-based chemotherapy were administered in 48 and 35 patients, respectively. Extent of resection was significantly associated with both overall survival (OS;  $p = 0.00$

96) and progression-free survival (PFS;  $p = 0.0007$ ) in patients with diffuse astrocytoma but not in those with oligodendroglial subtypes. Chemotherapy significantly prolonged PFS, especially in patients with oligodendroglial subtypes ( $p = 0.0009$ ). Patients with a mutant IDH1 gene had significantly longer OS ( $p = 0.034$ ). Multivariate analysis did not identify MIB-1 index or RT as prognostic factors, but it did identify chemotherapy as a prognostic factor for PFS and EOR as a prognostic factor for OS and PFS. CONCLUSIONS The findings demonstrated that EOR was significantly correlated with patient survival; thus, one should aim for maximum tumor resection. In addition, patients with a higher EOR can be safely observed without adjuvant therapy. For patients with partial resection, postoperative chemotherapy should be administered for those with oligodendroglial subtypes, and repeat resection should be considered for those with astrocytic tumors. More aggressive treatment with RT and chemotherapy may be required for patients with a poor prognosis, such as those with diffuse astrocytoma, 1p/19q nondeleted tumors, or IDH1 wild-type oligodendroglial tumors with partial resection.  
Journal Title: Neurosurgical focus

PUBMED ID: 25594327

DOI: doi.org/10.3171/2014.11.JNS13295

Titolo: Role of adjuvant or salvage radiosurgery in the management of unresected residual or progressive glioblastoma multiforme in the pre-bevacizumab era.

Autori: Niranjan A., Kano H., Iyer A., Kondziolka D., Flickinger JC., Lunsford LD.

Data di Pubblicazione: 2015-1-17

Abstract: In this analysis 30% of a heterogeneous cohort of GBM patients eligible for SRS had an OS of 2 years. Radiosurgery at the time of tumor progression was associated with a median survival of 21.8 months. The role of radiosurgery for GBMs remains controversial. The findings in this study support the need for a funded and appropriately designed clinical trial that will provide a higher level of evidence regarding the future role of SRS for glioblastoma patients in whom disease has progressed despite standard management.  
Journal Title: Journal of neurosurgery

PUBMED ID: 25575937

DOI: doi.org/10.1007/s11060-014-1693-x

Titolo: Impact of bevacizumab administered dose on overall survival of patients with progressive glioblastoma.

Autori: Levin VA., Mendelssohn ND., Chan J., Stovall MC., Peak SJ., Yee JL., Hui RL., Chen DM.

Data di Pubblicazione: 2015-1-11

Abstract: Bevacizumab (BEV, Avastin®) produces durable objective radiological responses of 20-26 %, median response durations of 16-18 weeks, and median overall survival (mOS) of 31-40 weeks. While the use of BEV is well-established, the lack of dose-response studies in glioblastoma (GBM) patients raises the question whether current dosing practice is optimal. As a result of differing approaches to BEV dosing that ranged from the FDA approved package insert dose of 10 mg/kg every 2 weeks to 7.5 mg/kg every 3-4 weeks, among physicians within Northern California Kaiser Permanente hospitals over 4+ years, we did an IRB-approved retrospective analysis of patients seen in Northern California Kaiser Permanente facilities and treated with BEV. Between September 1, 2008 and August 31, 2013, 181 patients received BEV for tumor progression/recurrence starting 2.6 weeks after completion of chemoradiation. The integrated BEV administered dose-week (AUCBEV) for all patients had a median AUCBEV of 3.6 mg·wk/kg. Maximum likelihood analysis found patients over 65 years did worse than younger patients ( $p = 0.004$ ), women lived longer ( $p = 0.002$ ), and patients treated below the AUCBEV did better than those treated a

bove the median AUCBEV ( $p = 0.003$ ). mOS for BEV starting 1 month after chemo radiation was 45 versus 68 weeks ( $p = 0.012$ ) and BEV starting 3 months after chemoradiation was 40 versus 74 weeks ( $p = 0.0085$ ). Dosing BEV at half the standard dose for progressive/recurrent GBM was at least equivalent to or, maybe better than standard dosing. Unexplained was the observation that females had longer OS with BEV than males.

Journal Title: Journal of neuro-oncology

PUBMED ID: 25572814

DOI: doi.org/10.1007/s12032-014-0460-3

Titolo: Single-agent bevacizumab is an effective treatment in recurrent glioblastoma.

Autori: Hacibekiroglu I., Kodaz H., Erdogan B., Turkmen E., Ozcelik M., Esenkaya A., Saygi HM., Uzunoglu S., Cicin I.

Data di Pubblicazione: 2015-1-10

Abstract: The aim of this study was to evaluate the efficiency and safety of single-agent bevacizumab therapy for recurrent glioblastoma multiforme (GBM). We identified patients with histologically confirmed glioblastoma and World Health Organization Grade III glioma who were previously treated with temozolomide plus radiotherapy and received 10 mg/kg bevacizumab intravenous infusion every 2 weeks until disease progression for recurrent disease. A total 24 patients included to this study. Twenty-two patients had GBM, and two patients had WHO grade III glioma. No complete response was observed, five patients (20.8 %) had partial response, nine patients (37.5 %) had stable diseases, and ten patients (41.7 %) had progressive diseases. The overall response rate was 20.8 %. The 6-month PFS rate (PFS6) and median PFS were determined as 37.5 % and 4.1 months, respectively. Median OS was 6.4 months. Performance status of 17 (70.8 %) patients was improved following bevacizumab regimen. Univariate analysis showed that improvement in performance status (IPS) following bevacizumab therapy was a significant predictor of both PFS ( $p < 0.001$ ) and OS ( $p < 0.020$ ). Bevacizumab-related adverse effects were observed in 13 (54.1 %) patients. Grade 3-4 toxicity was observed in 4 (16.6 %) patients. Therapy interruptions were experienced in two patients due to adverse effects. Single-agent bevacizumab is an effective and safe treatment alternative in recurrent GBM. IPS following bevacizumab therapy was a significant predictor of both PFS and OS.

Journal Title: Medical oncology (Northwood, London, England)

PUBMED ID: 25569296

DOI: doi.org/10.1016/j.clineuro.2014.12.006

Titolo: Gliomatosis cerebri having a poor performance status without recurrence after radiotherapy: a single institutional experience.

Autori: Jung TY., Yoon MS., Kim YH., Jung S., Kim IY., Jang WY., Moon KS., Lee KH., Kim SK.

Data di Pubblicazione: 2015-1-9

Abstract: Some GC patients, especially the elderly, might have a poor performance status without recurrence after RT of a larger radiation field.

Journal Title: Clinical neurology and neurosurgery

PUBMED ID: 25563816

DOI: doi.org/10.1007/s11060-014-1714-9

Titolo: Salvage therapy with lomustine for temozolomide refractory recurrent anaplastic astrocytoma: a retrospective study.

Autori: Chamberlain MC.

Data di Pubblicazione: 2015-1-8

Abstract: There is no standard therapy for recurrent anaplastic astrocytoma (AA). Assess response and toxicity of lomustine (CCNU) in recurrent AA follo

wing prior surgery, radiotherapy and TMZ in a retrospective case series. Thirty-five adults (18 males; 17 females: median age 42.5 years) with TMZ refractory recurrent AA were treated with lomustine. Seven patients were treated at 1st recurrence and 28 patients were treated at 2nd recurrence. Prior salvage therapy included re-resection in 19, TMZ in 20 and radiotherapy in 7. A cycle of lomustine was defined as 110 mg/m<sup>2</sup> on day 1 only administered once every 6-8 weeks. Success of treatment was defined as progression free survival at 6 months of 40 % or better. Grade 3 or 4 toxicities included anemia (14 patients), constipation (1), fatigue (4), lymphopenia (5), nausea/vomiting (2), neutropenia (8) and thrombocytopenia (10). No grade five toxicities were seen. The median number of cycles of therapy was 3 (range 1-6). Best radiographic response was progressive disease in 14 (40 %), stable disease in 19 (54 %) and partial response in 2 (5.7 %). Median progression free survival (PFS) was 4.5 months (range 1.5-12 months), 6-month PFS was 40 % and 12 month PFS was 11.4 %. Median survival after onset of CCNU was 9.5 months (range 2.5-15 months). Median overall survival was 2.7 years (range 1.7-4.3). In this small retrospective series of patients with recurrent AA refractory to TMZ, lomustine appears to have modest single agent with manageable toxicity. Confirmation in a larger series of similar patients is required.

Journal Title: Journal of neuro-oncology

PUBMED ID: 25555122

DOI: doi.org/10.3171/2014.9.PEDS14213

Titolo: Primitive neuroectodermal tumors of the brainstem in children treated according to the HIT trials: clinical findings of a rare disease.

Autori: Friedrich C., Warmuth-Metz M., von Bueren AO., Nowak J., Bison B., von Hoff K., Pietsch T., Kortmann RD., Rutkowski S.

Data di Pubblicazione: 2015-1-3

Abstract: CNS-PNET is a rare but important differential diagnosis in childhood brainstem tumors. So far, efficient therapies are lacking. The sampling of tumor material for improved biological understanding and identification of new therapeutic targets is important.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 27158638

DOI: doi.org/10.14800/ccm.747

Titolo: Temozolomide resistance and tumor recurrence: Halting the Hedgehog.

Autori: Munoz JL., Rodriguez-Cruz V., Walker ND., Greco SJ., Rameshwar P.

Data di Pubblicazione: 2016-5-10

Abstract: Chemotherapy with Temozolomide (TMZ), radiation and surgery are the primary methods to treat Glioblastoma Multiforme (GBM), the most common adult intracranial tumor with dismal outcome. GBM resistance to therapy is the main reason of poor patient outcomes. Thus, methods to overcome the resistance are an area of extensive research. This highlight focuses on three recently published articles on the mechanism of resistance and possible therapeutic intervention, including RNA treatment with stem cells. We showed a crucial role of the developmental Sonic Hedgehog (SHH) pathway in the acquisition and maintenance of TMZ resistance. SHH signaling caused TMZ resistance in GBM cells through an increase in the multiple drug resistance gene (MDR1). The SHH receptor, Patched-1 (PTCH1), negatively regulate SHH signaling. In GBM, miR-9 suppressed PTCH1 levels, resulting in the activation of SHH pathway. Thus, SHH signaling is independent of the ligand in resistant GBM cells. MiR-9 was also increased in chemoresistance CD133+ GBM cells. A potential method to reverse resistance was tested by delivering the anti-miR in bone marrow-derived Mesenchymal Stem Cells (MSCs). The anti-miR-9 was transferred into the resistant GBM cells through exosomes and gap junctional intercellular communication. We also review on-going clinical trials with inhibitor of SHH signaling, and also discuss drug delivery by cell therapy for GBM. While GBM treat

tment has proven to be a challenge, there are a number of novel approaches we are currently developing to manage this malignancy.

Journal Title: Cancer cell & microenvironment

PUBMED ID: 25542442

DOI: doi.org/10.1016/j.jfo.2014.06.011

Titolo: [Apropos of 5 cases of optic nerve tumors diagnosed during a 6-year-period].

Autori: Rebika S., Bonnin N., Kémény JL., Chiambaretta F., Bacin F.

Data di Pubblicazione: 2014-12-28

Abstract: The diagnosis of optic nerve tumors must be considered in cases of anterior or posterior progressive optic neuropathy. Treatment must be a compromise between effective treatment of the tumor and preservation of visual function. Decisions are made through multidisciplinary consultations, in which the role of the ophthalmologist is crucial for the diagnosis and success of the treatment.

Journal Title: Journal francais d'ophtalmologie

PUBMED ID: 25534576

DOI: doi.org/10.1007/s11060-014-1684-y

Titolo: Efficacy and patient-reported outcomes with dose-intense temozolomide in patients with newly diagnosed pure and mixed anaplastic oligodendroglioma: a phase II multicenter study.

Autori: Ahluwalia MS., Xie H., Dahiya S., Hashemi-Sadraei N., Schiff D., Fisher PG., Chamberlain MC., Pannullo S., Newton HB., Brewer C., Wood L., Prayson R., Elson P., Peereboom DM.

Data di Pubblicazione: 2014-12-24

Abstract: Standard initial therapy for patients with pure and mixed anaplastic oligodendrogliomas (AO/MAO) includes chemotherapy and radiation therapy. Anaplastic oligodendrogliomas with 1p/19q co-deletion are more responsive to chemotherapy. There is concern for potential long-term CNS toxicity of radiation. Hence an approach using chemotherapy initially and reserving radiation for progressive disease is attractive. This multicenter phase II trial included patients with newly diagnosed AO/MAO with central pathology review and 1p/19q assay. Temozolomide was given 150 mg/m<sup>2</sup> days 1-7 and 15-21, every 28 days for 8 cycles. The primary endpoint was progression free survival (PFS). Secondary endpoints included response rate, overall survival (OS), treatment toxicity and health-related quality of life (HRQL). Data from 62 patients enrolled between December 2001 and April 2007 at seven centers were analyzed. Among patients with measurable disease, 8 % achieved complete remission, 56 % had stable disease and 36 % had progression. The median PFS and OS were 27.2 months (95 % CI 11.9-36.3) and 105.8 months (95 % CI 51.5-N/A), respectively. Both 1p loss and 1p/19q co-deletion were positive prognostic factors for PFS (p < 0.001) and OS (p < 0.001); and there was some suggestion that 1p/19q co-deletion also predicted better response to chemotherapy (p = 0.007). Grade 3/4 toxicities were mainly hematological. Significantly improved HRQL in the future uncertainty domain of the brain cancer module was seen after cycle 4 (p < 0.001). This trial achieved outcomes similar to those reported previously. Toxicities from dose-intense temozolomide were manageable. Improvement in at least one HRQL domain increased over time. This trial supports the further study of first-line temozolomide monotherapy as an alternative to radiation therapy for patients with newly diagnosed AO/MAO with 1p/19q co-deleted tumors.

Journal Title: Journal of neuro-oncology

PUBMED ID: 25523732

DOI: doi.org/12.2014/JCPSP.935939



Titolo: Treatment updates regarding anaplastic oligodendroglioma and anaplastic oligoastrocytoma.

Autori: Khan KA., Abbasi AN., Ali N.

Data di Pubblicazione: 2014-12-20

Abstract: Anaplastic Oligodendroglioma / Anaplastic Oligoastrocytoma (AO/AOA) is a WHO Grade-III primary brain tumor. These tumors comprise about 5 - 10 % of all gliomas, which make them the third most common primary brain tumors after glioblastoma multiforme and astrocytomas. For many years standard of treatment remained Maximum Safe Resection (MSR) followed by Radiotherapy (RT). These tumors have also been known to be sensitive to alkylator-based chemotherapy particularly the subset having 1p/19q co-deletion signature. There is robust data showing that these tumors are responsive to chemotherapy in recurrent or progressive setting. Recently, up front chemotherapy has been added to standard post-surgery RT. It has been found that subset of AO/AOA having 1p/19q co-deletion responded very well to the addition of chemotherapy. This substantial benefit in terms of median Overall Survival (OS) and median Progression Free Survival (PFS) have intrigued the personalized treatment of AO/AOA on the basis of molecular signature markers.

Journal Title: Journal of the College of Physicians and Surgeons--Pakistan : JCPSP

PUBMED ID: 25493242

DOI: doi.org/10.5306/wjco.v5.i5.1060

Titolo: Clinicopathological features and treatment outcomes of brain stem gliomas in Saudi population.

Autori: Bayoumi Y., Sabbagh AJ., Mohamed R., ElShokhaiby UM., Maklad AM., Tounio MA., Balbaid AA.

Data di Pubblicazione: 2014-12-11

Abstract: BSG, especially the DIPG subgroup, had a dismal prognosis, needing more aggressive neurosurgical, radiation and chemotherapy techniques, while focal and tectal tumors were found to have a better prognosis.

Journal Title: World journal of clinical oncology

PUBMED ID: 25462098

DOI: doi.org/10.1016/j.clineuro.2014.11.006

Titolo: Treatment results and outcome in elderly patients with glioblastoma multiforme--a retrospective single institution analysis.

Autori: Hoffer mann M., Bruckmann L., Kariem Mahdy A., Asslaber M., Payer F., von Campe G.

Data di Pubblicazione: 2014-12-3

Abstract: It appears that more aggressive treatment regimens can lead to longer overall survival in elderly glioblastoma multiforme patients. Gross total resection should be offered whenever safely possible; otherwise, biopsy may be preferred. Non-surgical treatment should consist of postoperative radiotherapy and concomitant and/or adjuvant chemotherapy. Possibly higher rates of hematological side effects in concomitant chemotherapy need to be further investigated.

Journal Title: Clinical neurology and neurosurgery

PUBMED ID: 25441707

DOI: doi.org/10.1016/j.neuchi.2013.12.007

Titolo: Tectal plate tumours. Our experience with a paediatric surgical series.

Autori: Mottolese C., Szathmari A., Beuriat PA., Frappaz D., Jouvett A., Hermier M.

Data di Pubblicazione: 2014-12-3

Abstract: Exophytic tectal plate tumours can be treated based on a microsurgical approach in paediatric patients. In experienced hands surgery can be performed with an acceptable morbidity and with zero percent mortality. In our experience, the sub-occipital transtentorial approach permits a wide view of the region and safe surgical removal.

Journal Title: Neuro-Chirurgie

PUBMED ID: 25438813

DOI: doi.org/10.2217/cns.14.47

Titolo: Management of diffuse intrinsic pontine glioma in children: current and future strategies for improving prognosis.

Autori: Kaye EC., Baker JN., Broniscer A.

Data di Pubblicazione: 2014-12-3

Abstract: Diffuse intrinsic pontine glioma (DIPG) is one of the deadliest paediatric central nervous system cancers in spite of treatment with radiation therapy, the current standard of care. The outcome of affected children remains dismal despite multiple clinical trials that investigated radiation therapy combined with chemotherapy. Recently, multiple genome-wide studies unveiled the distinct molecular characteristics of DIPGs and preclinical models of DIPG were developed to mimic the human disease. Both of these accomplishments have generated tremendous progress in the research of new therapies for children with DIPG. Here we review some of these promising new strategies.

Journal Title: CNS oncology

PUBMED ID: 25434384

DOI: doi.org/10.3171/2014.9.FOCUS14519

Titolo: Molecularly targeted therapies for recurrent glioblastoma: current and future targets.

Autori: Lau D., Magill ST., Aghi MK.

Data di Pubblicazione: 2014-12-2

Abstract: Recurrent glioblastoma remains very difficult to treat, even with molecularly targeted therapies and anticancer agents. The currently available targeted therapy regimens have poor to modest activity against recurrent glioblastoma. As newer agents are actively being developed, combination regimens have provided the most promising results for improving outcomes. Targeted therapies matched to molecular profiles of individual tumors are predicted to be a critical component necessary for improving efficacy in future trials.

Journal Title: Neurosurgical focus

PUBMED ID: 25431212

DOI: doi.org/10.1093/neuonc/nou114

Titolo: A phase 1 and pharmacokinetic study of enzastaurin in pediatric patients with refractory primary central nervous system tumors: a pediatric brain tumor consortium study.

Autori: Kilburn LB., Kocak M., Decker RL., Wetmore C., Chintagumpala M., Su J., Goldman S., Banerjee A., Gilbertson R., Fouladi M., Kun L., Boyett JM., Blaney SM.

Data di Pubblicazione: 2014-11-29

Abstract: Enzastaurin was well tolerated in children with recurrent CNS malignancies, with chromaturia, fatigue, anemia, thrombocytopenia, and nausea being the most common toxicities. The recommended phase 2 dose is 440 mg/m<sup>2</sup>/day administered once daily.

Journal Title: Neuro-oncology

PUBMED ID: 25428586

DOI: doi.org/10.1007/s00234-014-1468-2

Titolo:  $^{23}\text{Na}$ -MRI of recurrent glioblastoma multiforme after intraoperative radiotherapy: technical note.

Autori: Haneder S., Giordano FA., Konstandin S., Brehmer S., Buesing KA., Schmiedek P., Schad LR., Wenz F., Schoenberg SO., Ong MM.

Data di Pubblicazione: 2014-11-28

Abstract: (23)Na-MRI provided similar information in the suspicious area compared to (18)F-FET-PET, exceeding conventional (1)H-MRI. Still, (23)Na-MRI remains an investigational technique, which is worth to be further evaluated.

Journal Title: Neuroradiology

PUBMED ID: 25424852

DOI: doi.org/10.1158/1078-0432.CCR-14-1380

Titolo: First-in-human dose study of the novel transforming growth factor- $\beta$  receptor I kinase inhibitor LY2157299 monohydrate in patients with advanced cancer and glioma.

Autori: Rodon J., Carducci MA., Sepulveda-Sánchez JM., Azaro A., Calvo E., Seoane J., Braña I., Sicart E., Gueorguieva I., Cleverly AL., Pillay NS., Desai D., Estrem ST., Paz-Ares L., Holdhoff M., Blakeley J., Lahn MM., Baselga J.

Data di Pubblicazione: 2014-11-27

Abstract: On the basis of the safety, pharmacokinetics, and antitumor activity in patients with glioma, the intermittent administration of LY2157299 at 300 mg/day is safe for future clinical investigation.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 25398846

DOI: doi.org/10.1158/1078-0432.CCR-14-0833

Titolo: Molecular insights into pediatric brain tumors have the potential to transform therapy.

Autori: Gajjar A., Pfister SM., Taylor MD., Gilbertson RJ.

Data di Pubblicazione: 2014-11-16

Abstract: High-throughput genomic technologies have shed light on the biologic heterogeneity of several pediatric brain tumors. The biology of the four common pediatric brain tumors—namely medulloblastoma; ependymoma; high-grade glioma (HGG), including diffuse intrinsic pontine glioma; and low-grade glioma—is highlighted in this CCR Focus article. The discovery that medulloblastoma consists of four different subgroups, namely WNT, SHH, Group 3, and Group 4, each with distinct clinical and molecular features, has affected the treatment of children with medulloblastoma. Prospective studies have documented the efficacy of SMO inhibitors in a subgroup of patients with SHH medulloblastoma. Efforts are ongoing to develop specific therapies for each of the subgroups of medulloblastoma. Similar efforts are being pursued for ependymoma, HGG, and diffuse intrinsic pontine glioma where the disease outcome for the latter two tumors has not changed over the past three decades despite several prospective clinical trials. Developing and testing targeted therapies based on this new understanding remains a major challenge to the pediatric neuro-oncology community. The focus of this review is to summarize the rapidly evolving understanding of the common pediatric brain tumors based on genome-wide analysis. These novel insights will add impetus to translating these laboratory-based discoveries to newer therapies for children diagnosed with these tumors.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 25375042

DOI: Mancante

Titolo: Multidisciplinary management of adult low grade gliomas.

Autori: Mariş D., Nica D., Mohan D., Moisa H., Ciurea AV.

Data di Pubblicazione: 2014-11-7

Abstract: LGG: low grade gliomas, WHO: World Health Organization, OS: overall survival, PFS: progression-free survival, MRI: Magnetic resonance imaging, MRS: Magnetic resonance spectroscopy, MPFS: malignant progression-free survival, rCBV: Relative Cerebral Blood Volume, QOL: quality of life, FLAIR: Fluid attenuated inversion recovery, MGMT: O6-methylguanine DNA methyltransferase enzyme, DSC MR imaging: Dynamic Susceptibility Contrast Perfusion MR imaging, 1H-MRS: Proton Magnetic Resonance Spectroscopy, IDH1: isocitrate dehydrogenase 1 gene, SPECT: Single-photon emission computed tomography, PET: Positron emission tomography, DTI-FT: Diffuse Tensor Imaging-fiber tracking technique, DES: direct electrical stimulation, EEG: Electroencephalography, EcoG: Electrocorticography, MEP: motor evoked potentials, EMG: Electromyography, AED: anti-epileptic drugs, TMZ: Temozolomide, EORTC: European Organization for Research and Treatment of Cancer, NCCTG: North Central Cancer Treatment Group, RTOG: Radiation Therapy Oncology Group, ECOG: Eastern Cooperative Oncology Group, EOR: extent of resection, Gy: Gray (unit), GyE: gray equivalent, RT: radiation therapy, IMRT: image-guided intensity modulated radiotherapy, FSRT: fractionated stereotactic radiotherapy, SRS: proton therapy or stereotactic radiosurgery, LET: high-linear energy transfer beams, RBE: relative biological effectiveness, CTCAE: Common Terminology Criteria for Adverse Events, PCV: procarbazine, lomustine, and vincristine chemotherapy.

Journal Title: Chirurgia (Bucharest, Romania : 1990)

PUBMED ID: 25366366

DOI: doi.org/10.1007/s11060-014-1652-6

Titolo: Single agent vinorelbine in pediatric patients with progressive optic pathway glioma.

Autori: Cappellano AM., Petrilli AS., da Silva NS., Silva FA., Paiva PM., Calvalheiro S., Bouffet E.

Data di Pubblicazione: 2014-11-5

Abstract: The management of progressive unresectable low-grade glioma remains controversial. Treatment options have included radiotherapy, and more recently chemotherapy, usually following an initial period of observation. Within this context, we evaluated vinorelbine, a semi-synthetic vinca alkaloid that has shown evidence of activity against glioma. From July 2007 an institutional protocol with vinorelbine (30 mg/m<sup>2</sup> days 0, 8, 22) for a total of 18 cycles, has been conducted at IOP/GRAACC/UNIFESP for children with optic pathway glioma (OPG). The main objectives were clinical and radiological response, as well as toxicity profile. Twenty-three patients with progressive OPG with a mean age of 69 months (4-179) were enrolled. Three patients had a diagnosis of neurofibromatosis type 1. Twenty-two patients were assessable for response with an overall objective response rate of 63 %, with eight patients showing stable disease. The most important toxicity was hematologic (grade III/IV neutropenia) observed in four patients. Gastrointestinal toxicity (grade I/II vomiting) was observed in seven patients and only 1 patient showed grade I peripheral neuropathy. The median progression-free survival (PFS) was 33 months (6.9-69) with a 3 and 5 year PFS of 64 ± 19 and 37 ± 20 %, respectively, for an overall 3 and 5 year-survival of 95 ± 10 %. This study suggests that vinorelbine may be an interesting option for pediatric low-grade gliomas, showing low toxicity profile and providing a good quality of life for patients with such chronic disease.

Journal Title: Journal of neuro-oncology

PUBMED ID: 25366336

DOI: doi.org/10.1093/neuonc/nou303

Titolo: Preclinical antitumor efficacy of selective exportin 1 inhibitors in glioblastoma.

Autori: Green AL., Ramkissoon SH., McCauley D., Jones K., Perry JA., Hsu JH., Ramkissoon LA., Maire CL., Hubbell-Engler B., Knoff DS., Shacham S., Ligon KL., Kung AL.

Data di Pubblicazione: 2014-11-5

Abstract: SINE compounds show preclinical efficacy utilizing in vitro and in vivo models of GBM, with induction of apoptosis as the mechanism of action. Selinexor is now in early clinical trials in solid and hematological malignancies. Based on these preclinical data and excellent brain penetration, we have initiated clinical trials of Selinexor in patients with relapsed GBM.

Journal Title: Neuro-oncology

PUBMED ID: 25355680

DOI: doi.org/10.1093/neuonc/nou297

Titolo: Practice changing mature results of RTOG study 9802: another positive PCV trial makes adjuvant chemotherapy part of standard of care in low-grade glioma.

Autori: van den Bent MJ.

Data di Pubblicazione: 2014-10-31

Abstract: The long-term follow-up of the RTOG 9802 trial that compared 54 Gy of radiotherapy (RT) with the same RT followed by adjuvant procarbazine, CCNU, and vincristine (PCV) chemotherapy in high-risk low-grade glioma shows a major increase in survival after adjuvant PCV chemotherapy. Median overall survival increased from 7.8 years to 13.3 years, with a hazard ratio of death of 0.59 (log rank:  $P = .002$ ). This increase in survival was observed despite the fact that 77% of patients who progressed after RT alone received salvage chemotherapy. With this outcome, RT + PCV is now to be considered standard of care for low-grade glioma requiring postsurgical adjuvant treatment. Unfortunately, studies on molecular correlates associated with response are still lacking. This is now the third trial showing benefit from the addition of PCV to RT in grade II or III diffuse glioma. The optimal parameter for selecting patients for adjuvant PCV has not yet been fully elucidated, but several candidate markers have so far emerged. It is still unclear whether temozolomide can replace PCV and whether initial management with chemotherapy only is a safe initial treatment. Potentially, that may adversely affect overall survival, but concerns for delayed RT-induced neurotoxicity may limit acceptance of early RT in patients with expected long term survival. The current evidence supports that in future trials, grades II and III tumors with similar molecular backgrounds should be combined, and trials should focus on molecular glial subtype regardless of grade.

Journal Title: Neuro-oncology

PUBMED ID: 25342602

DOI: doi.org/10.1093/neuonc/nou232

Titolo: Targeted molecular therapies against epidermal growth factor receptor: past experiences and challenges.

Autori: Reardon DA., Wen PY., Mellinghoff IK.

Data di Pubblicazione: 2014-10-25

Abstract: Epidermal growth factor receptor (EGFR) has emerged as a highly attractive therapeutic target in glioblastoma (GBM) based on its high frequency of gene amplification and mutation and its identification as an upstream trigger of dysregulated cell signaling cascades that drive GBM pathophysiology. Extensive investment has been committed in an attempt to exploit EGFR therapeutically to improve outcome for GBM patients, including the development of a variety of EGFR-targeting therapeutics as well as the participation of hundreds of participants in multiple, carefully constructed clinical trials. In this review, we summarize the design and results of clinical trials evalu

ating EGFR tyrosine kinase inhibitors in recurrent and newly diagnosed GBM patients. While overall results thus far have been disappointing, it is premature to discount EGFR as a therapeutic target in GBM on the basis of these studies given the limitations in study design and the pharmacology of first-generation EGFR kinase inhibitors. Although important lessons have been learned, critical questions remain unanswered and warrant further study.

Journal Title: Neuro-oncology

PUBMED ID: 25338498

DOI: doi.org/10.1158/1078-0432.CCR-14-0951-T

Titolo: A phase II, randomized, study of weekly APG101+reirradiation versus reirradiation in progressive glioblastoma.

Autori: Wick W., Fricke H., Junge K., Kobayakov G., Martens T., Heese O., Wiestler B., Schliesser MG., von Deimling A., Pichler J., Vetlova E., Harting I., Debus J., Hartmann C., Kunz C., Platten M., Bendszus M., Combs SE.

Data di Pubblicazione: 2014-10-24

Abstract: CD95 pathway inhibition in combination with rRT is an innovative concept with clinical efficacy. It warrants further clinical development. CD95L promoter methylation in the tumor may be developed as a biomarker.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 25325421

DOI: doi.org/10.3171/2014.9.PEDS1462

Titolo: Neurosurgical treatment of pediatric low-grade midbrain tumors: a single consecutive institutional series of 15 patients.

Autori: Lundar T., Due-Tønnessen BJ., Egge A., Scheie D., Brandal P., Stensvold E., Due-Tønnessen P.

Data di Pubblicazione: 2014-10-18

Abstract: Selected cases of low-grade midbrain gliomas may clearly benefit from resection with favorable results, even for prolonged periods. Three patients in the present series died, one of whom had a prolonged survival period of 21 years. Among the 12 survivors, stable long-term results appeared obtainable in at least 9. One patient died of acute hemorrhage 8 months after initial resection; otherwise, rapid tumor progression and death were not observed. Forty percent of the patients received adjuvant treatment, with local radiotherapy, chemotherapy, or both.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 25286037

DOI: doi.org/10.2217/cns.14.29

Titolo: Retrospective analysis of safety and feasibility of a 3 days on/11 days off temozolomide dosing regimen in recurrent adult malignant gliomas.

Autori: van Vugt VA., Piccioni DE., Brown BD., Brown T., Saria MG., Juarez T., Kesari S.

Data di Pubblicazione: 2014-10-7

Abstract: The '3 on/11 off' temozolomide regimen for recurrent high-grade gliomas was tolerable and warrants further study in a larger, prospective study.

Journal Title: CNS oncology

PUBMED ID: 25277867

DOI: doi.org/10.1159/000366167

Titolo: Can multiparametric MRI and FDG-PET predict outcome in diffuse brain stem glioma? A report from a prospective phase-II study.

Autori: Goda JS., Dutta D., Raut N., Juvekar SL., Purandare N., Rangarajan V., Arora B., Gupta T., Kurkure P., Jalali R.

Data di Pubblicazione: 2014-10-4

Abstract: Cumulative RPI was able to classify tumours into different grades and predicted clinical outcome. At baseline, MR hyperperfusion indicated a shorter survival for DIPG patients. Sensitivity and specificity of imaging modalities to detect low-grade gliomas were poor.

Journal Title: Pediatric neurosurgery

PUBMED ID: 25268364

DOI: doi.org/10.1371/journal.pone.0108861

Titolo: Human cytomegalovirus tegument protein pp65 is detected in all intra- and extra-axial brain tumours independent of the tumour type or grade.

Autori: Libard S., Popova SN., Amini RM., Kärjä V., Pietiläinen T., Hämäläinen KM., Sundström C., Hesselager G., Bergqvist M., Ekman S., Zetterling M., Smits A., Nilsson P., Pfeifer S., de Ståhl TD., Enblad G., Ponten F., Alafuzoff I.

Data di Pubblicazione: 2014-10-1

Abstract: Human cytomegalovirus (HCMV) has been indicated being a significant oncomodulator. Recent reports have suggested that an antiviral treatment alters the outcome of a glioblastoma. We analysed the performance of commercial HCMV-antibodies applying the immunohistochemical (IHC) methods on brain samples obtained from a subject with a verified HCMV infection, on samples obtained from 14 control subjects, and on a tissue microarray block containing cores of various brain tumours. Based on these trials, we selected the best performing antibody and analysed a cohort of 417 extra- and intra-axial brain tumours such as gliomas, medulloblastomas, primary diffuse large B-cell lymphomas, and meningiomas. HCMV protein pp65 immunoreactivity was observed in all types of tumours analysed, and the IHC expression did not depend on the patient's age, gender, tumour type, or grade. The labelling pattern observed in the tumours differed from the labelling pattern observed in the tissue with an active HCMV infection. The HCMV protein was expressed in up to 90% of all the tumours investigated. Our results are in accordance with previous reports regarding the HCMV protein expression in glioblastomas and medulloblastomas. In addition, the HCMV protein expression was seen in primary brain lymphomas, low-grade gliomas, and in meningiomas. Our results indicate that the HCMV protein pp65 expression is common in intra- and extra-axial brain tumours. Thus, the assessment of the HCMV expression in tumours of various origins and pathologically altered tissue in conditions such as inflammation, infection, and even degeneration should certainly be facilitated.

Journal Title: PloS one

PUBMED ID: 25261659

DOI: Mancante

Titolo: Characteristics of childhood glial tumors, management approaches and life expectancy of the patients.

Autori: Arslan A., Guney Y., Cihan YB., Cetindag MF.

Data di Pubblicazione: 2014-9-28

Abstract: Low-grade disease and total/gross total resection prolong PFS and OS in patients with childhood glial tumors.

Journal Title: Journal of B.U.ON. : official journal of the Balkan Union of Oncology

PUBMED ID: 25261556

DOI: doi.org/10.1158/1078-0432.CCR-14-1143

Titolo: An open-label phase Ib dose-escalation study of TRC105 (anti-endoglin antibody) with bevacizumab in patients with advanced cancer.

Autori: Gordon MS., Robert F., Matei D., Mendelson DS., Goldman JW., Chiorean EG., Strother RM., Seon BK., Figg WD., Peer CJ., Alvarez D., Adams BJ., Thuermer CP., Rosen LS.

Data di Pubblicazione: 2014-9-28

Abstract: TRC105 was well tolerated with bevacizumab and clinical activity was observed in a VEGF inhibitor-refractory population. Ongoing clinical trials are testing TRC105 in combination with bevacizumab in glioblastoma and with VEGFR TKIs in renal cell carcinoma, hepatocellular carcinoma, and soft tissue sarcoma.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 25247196

DOI: doi.org/10.1155/2014/952128

Titolo: Interleukin-13 receptor alpha 2-targeted glioblastoma immunotherapy.

Autori: Sengupta S., Thaci B., Crawford AC., Sampath P.

Data di Pubblicazione: 2014-9-24

Abstract: Glioblastoma (GBM) is the most lethal primary brain tumor, and despite several refinements in its multimodal management, generally has very poor prognosis. Targeted immunotherapy is an emerging field of research that shows great promise in the treatment of GBM. One of the most extensively studied targets is the interleukin-13 receptor alpha chain variant 2 (IL13R $\alpha$ 2). Its selective expression on GBM, discovered almost two decades ago, has been a target for therapy ever since. Immunotherapeutic strategies have been developed targeting IL13R $\alpha$ 2, including monoclonal antibodies as well as cell-based strategies such as IL13R $\alpha$ 2-pulsed dendritic cells and IL13R $\alpha$ 2-targeted chimeric antigen receptor-expressing T cells. Advanced therapeutic development has led to the completion of several clinical trials with promising outcomes. In this review, we will discuss the recent advances in the IL13R $\alpha$ 2-targeted immunotherapy and evaluate the most promising strategy for targeted GBM immunotherapy.

Journal Title: BioMed research international

PUBMED ID: 25242542

DOI: doi.org/10.1002/14651858.CD008218.pub3

Titolo: Antiangiogenic therapy for high-grade glioma.

Autori: Khasraw M., Ameratunga MS., Grant R., Wheeler H., Pavlakis N.

Data di Pubblicazione: 2014-9-23

Abstract: In patients with newly diagnosed GBM, the use of antiangiogenic therapy does not improve survival, despite evidence of improved progression-free survival. Thus at this time, evidence is insufficient to support the use of antiangiogenic therapy in patients with newly diagnosed GBM on the basis of effects on survival. Bevacizumab may confer a progression-free survival benefit in GBM; however evidence in favour of using other antiangiogenic therapies in recurrent GBM is insufficient. Although bevacizumab appears to prolong progression-free survival in newly diagnosed and recurrent GBM, the impact of this on quality of life remains unclear. Adequately powered, randomised, placebo-controlled studies of bevacizumab in recurrent GBM (or HGG) are needed. Not addressed here is whether subsets of patients with newly diagnosed GBM may benefit from antiangiogenic therapies and whether these therapies are useful in other high-grade glioma histologies.

Journal Title: The Cochrane database of systematic reviews

PUBMED ID: 25241615

DOI: doi.org/10.4274/Jcrpe.1306

Titolo: A case of central precocious puberty due to concomitant hypothalamic hamartoma and juvenile pilocytic astrocytoma.



Autori: Çatlı G., Abacı A., Anık A., Güler yüz H., Özer E., Öcal I., Yüceer N., Mutafoğlu K.

Data di Pubblicazione: 2014-9-23

Abstract: Central precocious puberty (CPP) is caused by premature activation of the hypothalamo-pituitary-gonadal axis. More than 50% of boys with CPP have an identifiable etiology. Hypothalamic hamartoma (HH), hydrocephalus, tumors, infections, congenital defects, ischemia, radiation, or injury of the brain are the most common causes of secondary CPP. In this report, we present the case of a 2 years and 9 months old male patient who had a 30x40 mm contrast-enhancing suprasellar mass and was histopathologically diagnosed with giant HH. However, since HHs are designated as non-enhancing masses, considering the possibility of an incomplete diagnosis of a glial tumor, the patient was followed up. Clinical and radiological follow-up revealed stable findings with no evidence of tumor growth until the third year after surgery when he presented with neurological deficit due to the rapid growth of the suprasellar mass. After the second surgery, histopathological examination of the biopsy specimen revealed the lesion to be a juvenile pilocytic astrocytoma (PA). The concomitance of HH and juvenile PA is very rare. To our knowledge, this is the first report of a patient with concomitant juvenile PA and HH who developed CPP and did not have gelastic epilepsy despite the rapidly growing giant mass.

Journal Title: Journal of clinical research in pediatric endocrinology

PUBMED ID: 25228535

DOI: doi.org/10.1177/1534735414550037

Titolo: Spinal cord stimulation as adjuvant during chemotherapy and reirradiation treatment of recurrent high-grade gliomas.

Autori: Clavo B., Robaina F., Jorge IJ., Cabrera R., Ruiz-Egea E., Szolna A., Otermin E., Llontop P., Carames MA., Santana-Rodríguez N., Sminia P.

Data di Pubblicazione: 2014-9-18

Abstract: Spinal cord stimulation during reirradiation and chemotherapy is feasible and well tolerated. In our study, spinal cord stimulation was associated with clinical improvement and longer survival than previously reported in recurrent anaplastic gliomas. Spinal cord stimulation as adjuvant during chemotherapy and reirradiation in relapsed HGGs merits further research.

Journal Title: Integrative cancer therapies

PUBMED ID: 25192475

DOI: doi.org/10.3171/2014.7.JNS132449

Titolo: Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma.

Autori: Grabowski MM., Recinos PF., Nowacki AS., Schroeder JL., Angelov L., Barnett GH., Vogelbaum MA.

Data di Pubblicazione: 2014-9-6

Abstract: CE-RTV and EOR were found to be significant predictors of survival after GBM resection. CERTV was the more significant predictor of survival compared with EOR, suggesting that the volume of residual contrast-enhancing tumor may be a more accurate and meaningful reflection of the pathobiology of GBM.

Journal Title: Journal of neurosurgery

PUBMED ID: 25151509

DOI: doi.org/10.1007/s11060-014-1595-y

Titolo: Low-dose rate stereotactic iodine-125 brachytherapy for the treatment of inoperable primary and recurrent glioblastoma: single-center experience with 201 cases.

Autori: Kickingeder P., Hamisch C., Suchorska B., Galldiks N., Visser-Vandewalle V., Goldbrunner R., Kocher M., Treuer H., Voges J., Ruge MI.

Data di Pubblicazione: 2014-8-25

Abstract: Treatment options for inoperable glioblastoma are limited. Low-dose-rate stereotactic iodine-125 brachytherapy (SBT) has been reported as an effective and low-risk treatment option for circumscribed low-grade gliomas and brain metastases. The present study evaluates this treatment approach for patients with inoperable glioblastoma. Between 1990 and 2012, 201 patients with histologically proven glioblastoma were treated with SBT (iodine-125 seeds; median cumulative surface dose, 60 Gy; median dose-rate, 6 cGy/h; median gross-tumor-volume, 17 ml) either as primary treatment (n = 103) or at recurrence (n = 98). In addition to SBT, 90.3 % of patients in the primary treatment group received external boost radiotherapy (median dose, 25.2 Gy). Adjuvant chemotherapy was added for 30.8 % of patients following SBT and consisted of temozolomide for the majority of cases (88.7 %). Procedure-related complications, clinical outcome, progression-free and overall survival (PFS, OS) were evaluated. Median follow-up was 9.8 months. The procedure-related mortality was zero. During follow-up, transient and permanent procedure-related morbidity was observed in 7.5 and 2.0 %, respectively. Calculated from the time of SBT, median OS and PFS rates were 10.5 and 6.2 months, with no significant differences among primary and recurrent tumors (11.1 vs. 10.4 months for OS and 6.2 vs. 5.9 months for PFS). For OS, multivariate analysis revealed Karnofsky performance score, age, and adjuvant chemotherapy as independent prognostic factors (all p < 0.01). Low-dose-rate SBT is a relatively safe and potentially effective local treatment option for patients with circumscribed inoperable glioblastoma initially or at recurrence. It deserves prospective validation since it may improve the outcome for a subset of patients with inoperable GBM.

Journal Title: Journal of neuro-oncology

PUBMED ID: 25139026

DOI: doi.org/10.1007/s11060-014-1589-9

Titolo: Temozolomide after radiotherapy in recurrent "low grade" diffuse brainstem glioma in adults.

Autori: Reyes-Botero G., Laigle-Donadey F., Mokhtari K., Martin-Duverneuil N., Delattre JY.

Data di Pubblicazione: 2014-8-21

Abstract: Diffuse brainstem glioma is a rare disease in adults. Radiotherapy (RT) is usually considered to be the standard treatment. However, the role of chemotherapy in treating relapses after RT is unclear, and this study aimed to assess the use of temozolomide (TMZ) in this situation. We conducted a retrospective analysis of patients from our database with "low grade" adult diffuse infiltrating brainstem glioma who received TMZ at relapse after failing RT. The patients were diagnosed by histology or MRI criteria compatible with a low-grade glioma. The tumors were localized in the pons, medulla oblongata or midbrain, excluding supratentorial or infratentorial tumors that had infiltrated the brainstem secondarily. The patients' clinical and radiological responses were assessed, and their progression free survival (PFS) and overall survival (OS) time were estimated. Fifteen adult patients (median age 34 years) fulfilled the inclusion criteria. Histological analysis was available in 5 cases and showed grade II oligodendroglioma (2 cases), grade II oligoastrocytoma (2 cases), and grade II astrocytoma (1 case). Ten patients were selected by MRI criteria only. All patients received RT as initial treatment and had a median PFS of 34.2 months (95 % CI 24.1-44.2). The median KPS at the time of relapse was 80. TMZ was administered orally at 150-200 mg/m<sup>2</sup> for 5 days, every 28 days. Clinical improvement after TMZ was observed in 9 cases (60 %), whereas radiological assessment detected responses in 6/15 cases, including 4 partial and 2 minor responses. The estimated median PFS after TMZ was 9.5 months (95 % CI 7.9-11), and the median OS was 14.4 months (

95 % CI 10.5-18.2). Grade 3 thrombopenia was observed in 26 % of cases. TMZ could be useful after RT failure in adult patients with recurrent diffuse "low grade" brainstem glioma.

Journal Title: Journal of neuro-oncology

PUBMED ID: 25137883

DOI: Mancante

Titolo: Clinical outcome of postoperative radiotherapy with or without chemotherapy in adult glioblastoma multiforme in Ramathibodi Hospital: a retrospective study.

Autori: Puddhikarant P., Swangsilpa T., Dhanachai M., Narkwong L., Sitathane C., Puataweepong P., Jiarpinitnun C., Witoonpanich P., Ruangkanchanasetr R.

Data di Pubblicazione: 2014-8-21

Abstract: Proper management of GBM patient was surgical removal and postoperative radiotherapy with or without chemotherapy. Proper palliative treatment modality was considered in selected cases of recurrent or progressive disease.

Journal Title: Journal of the Medical Association of Thailand = Chotmaihet thangphaet

PUBMED ID: 25107913

DOI: doi.org/10.1158/1078-0432.CCR-14-0822

Titolo: Phase II study of bevacizumab, temozolomide, and hypofractionated stereotactic radiotherapy for newly diagnosed glioblastoma.

Autori: Omuro A., Beal K., Gutin P., Karimi S., Correa DD., Kaley TJ., DeAngelis LM., Chan TA., Gavrilovic IT., Nolan C., Hormigo A., Lassman AB., Mellingerhoff I., Grommes C., Reiner AS., Panageas KS., Baser RE., Tabar V., Pentsova E., Sanchez J., Barradas-Panchal R., Zhang J., Faivre G., Brennan CW., Abrey LE., Huse JT.

Data di Pubblicazione: 2014-8-10

Abstract: This aggressive radiotherapy schedule was safe and more convenient for patients, achieving an OS that is comparable with historical controls. Analysis of advanced neuroimaging parameters suggests ADC and FDG-PET as potentially useful biomarkers, whereas tissue correlatives uncovered the poor prognosis associated with the proneural signature in non-IDH-1-mutated glioblastoma.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 25096071

DOI: doi.org/10.1007/s00381-014-2513-5

Titolo: Main editor's comment to the paper: the response and survival of children with recurrent diffuse intrinsic pontine glioma based on phase II study of antineoplastons A10 and AS2-1 in patients with brainstem glioma. Stanislaw R. Burzynski, Tomasz J. Janicki, Gregory S. Burzynski, Ania Marszalek.

Autori: Di Rocco C.

Data di Pubblicazione: 2014-8-7

Abstract:

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 25087230

DOI: doi.org/10.1093/neuonc/nou153

Titolo: New concepts in the management of diffuse low-grade glioma: Proposal of a multistage and individualized therapeutic approach.

Autori: Duffau H., Taillandier L.

Data di Pubblicazione: 2014-8-4

Abstract: Diffuse low-grade glioma grows, migrates along white matter tracts, and progresses to high-grade glioma. Rather than a "wait and see" policy, an aggressive attitude is now recommended, with early surgery as the first therapy. Intraoperative mapping, with maximal resection according to functional boundaries, is associated with a longer overall survival (OS) while minimizing morbidity. However, most studies have investigated the role of only one specific treatment (surgery, radiotherapy, chemotherapy) without taking a global view of managing the cumulative time while preserving quality of life (QoL) versus time to anaplastic transformation. Our aim is to switch towards a more holistic concept based upon the anticipation of a personalized and long-term multistage therapeutic approach, with online adaptation of the strategy over the years using feedback from clinical, radiological, and histomolecular monitoring. This dynamic strategy challenges the traditional approach by proposing earlier therapy, by repeating treatments, and by reversing the classical order of therapies (eg, neoadjuvant chemotherapy when maximal resection is impossible, no early radiotherapy) to improve OS and QoL. New individualized management strategies should deal with the interactions between the course of this chronic disease, reaction brain remapping, and oncofunctional modulation elicited by serial treatments. This philosophy supports a personalized, functional, and preventive neuro-oncology.

Journal Title: Neuro-oncology

PUBMED ID: 25080363

DOI: doi.org/10.1002/cncr.28907

Titolo: Reirradiation of recurrent medulloblastoma: does clinical benefit outweigh risk for toxicity?

Autori: Wetmore C., Herington D., Lin T., Onar-Thomas A., Gajjar A., Merchant TE.

Data di Pubblicazione: 2014-8-1

Abstract: The use of irradiation as a component of salvage therapy for relapsed MB may prolong survival. The benefit appears to be greatest for relapsed standard-risk patients.

Journal Title: Cancer

PUBMED ID: 25079885

DOI: doi.org/10.1007/s00381-014-2511-7

Titolo: Commentary: The response and survival of children with recurrent diffuse intrinsic pontine glioma based on phase II study of antineoplastic A10 and AS2-1 in patients with brainstem glioma, by Burzynski G, et al.

Autori: Massimino M., Clerici CA.

Data di Pubblicazione: 2014-8-1

Abstract:

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 25078721

DOI: doi.org/10.1016/j.addr.2014.07.010

Titolo: Multimodal imaging of gliomas in the context of evolving cellular and molecular therapies.

Autori: Keunen O., Taxt T., Grüner R., Lund-Johansen M., Tonn JC., Pavlin T., Bjerkvig R., Niclou SP., Thorsen F.

Data di Pubblicazione: 2014-8-1

Abstract: The vast majority of malignant gliomas relapse after surgery and standard radio-chemotherapy. Novel molecular and cellular therapies are thus being developed, targeting specific aspects of tumor growth. While histopath

ology remains the gold standard for tumor classification, neuroimaging has over the years taken a central role in the diagnosis and treatment follow up of brain tumors. It is used to detect and localize lesions, define the target area for biopsies, plan surgical and radiation interventions and assess tumor progression and treatment outcome. In recent years the application of novel drugs including anti-angiogenic agents that affect the tumor vasculature, has drastically modulated the outcome of brain tumor imaging. To properly evaluate the effects of emerging experimental therapies and successfully support treatment decisions, neuroimaging will have to evolve. Multi-modal imaging systems with existing and new contrast agents, molecular tracers, technological advances and advanced data analysis can all contribute to the establishment of disease relevant biomarkers that will improve disease management and patient care. In this review, we address the challenges of glioma imaging in the context of novel molecular and cellular therapies, and take a prospective look at emerging experimental and pre-clinical imaging techniques that bear the promise of meeting these challenges.

Journal Title: Advanced drug delivery reviews

PUBMED ID: 25065849

DOI: doi.org/10.1016/j.jocn.2014.03.034

Titolo: Spinal metastasis of gliosarcoma: array-based comparative genomic hybridization for confirmation of metastatic spread.

Autori: Schindler G., Capper D., Korshunov A., Schmieder K., Brenke C.

Data di Pubblicazione: 2014-7-29

Abstract: We report a 64-year-old woman who underwent craniotomy and gross total resection of a left frontal lobe tumor initially diagnosed as glioblastoma. Multiple wound revisions were necessary due to repeated wound healing disorders under concomitant radio-chemotherapy. After 9 months there was local cranial tumor recurrence, requiring re-operation. Thereafter, temozolomide monotherapy was implemented. Histologically, a shift from glial to mesenchymal differentiation was observed in the recurrent tumor, resulting in the diagnosis of gliosarcoma. A further 9 months later a thoracic spinal tumor occurred requiring emergency tumor resection. Analysis showed a mesenchymal tumor without definite glial component. Being resistant to local radiation therapy, symptomatic local spinal tumor progression was observed within 1 month requiring re-resection. There was no response to chemotherapy with bevacizumab and irinotecan. Considering the pronounced sarcoma-like differentiation, a sarcoma chemotherapy regime with doxorubicin was initiated. This was also to no avail; the disease progressed and recurred at both the spinal and cerebral locations, respectively. This ambiguous tumor characteristic and therapy resistance encouraged us to retrospectively perform molecular and array-based comparative genomic hybridization (aCGH) analysis on the extirpated cerebral and spinal tumors. Tumors from both locations showed a consistent cytogenetic signature of gain of chromosome 7, and losses of chromosomes 10 and 13. This novel report of aCGH analysis of spinal gliosarcoma metastasis and the correlation to the clinical disease course shows that genotypic profiling may serve as a supplementary diagnostic tool in improving our knowledge of the biologic behavior of rare tumor variants.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 25055819

DOI: doi.org/10.1136/jnnp-2014-308136

Titolo: Seizure reduction in a low-grade glioma: more than a beneficial side effect of temozolomide.

Autori: Koekkoek JA., Dirven L., Heimans JJ., Postma TJ., Vos MJ., Reijneveld JC., Taphoorn MJ.

Data di Pubblicazione: 2014-7-25

Abstract: TMZ may contribute to an important reduction in seizure frequency in patients with LGG. Seizure reduction following TMZ treatment has prognostic significance and may serve as an important clinical outcome measure in patients with LGG.

Journal Title: Journal of neurology, neurosurgery, and psychiatry

PUBMED ID: 25047029

DOI: doi.org/10.1007/s00401-014-1319-6

Titolo: Histopathological spectrum of paediatric diffuse intrinsic pontine glioma: diagnostic and therapeutic implications.

Autori: Buczkowicz P., Bartels U., Bouffet E., Becher O., Hawkins C.

Data di Pubblicazione: 2014-7-23

Abstract: Diffuse intrinsic pontine glioma (DIPG) is the main cause of brain tumour-related death in children. In the majority of cases diagnosis is based on clinical and MRI findings, resulting in the scarcity of pre-treatment specimens available to study. Our group has developed an autopsy-based protocol to investigate the histologic and biologic spectrum of DIPG. This has also allowed us to investigate the terminal pattern of disease and gain a better understanding of what challenges we are facing in treating DIPG. Here, we review 72 DIPG cases with well documented clinical history and molecular data and describe the pathological features of this disease in relation to clinical and genetic features. Fifty-three of the samples were autopsy material (7 pre-treatment) and 19 were pre-treatment biopsy/surgical specimens. Upon histological review, 62 patients had high-grade astrocytomas (18 WHO grade I-II and 44 WHO grade IV patients), 8 had WHO grade II astrocytomas, and 2 had features of primitive neuroectodermal tumour (PNET). K27M-H3 mutations were exclusively found in tumours with WHO grade II-IV astrocytoma histology. K27M-H3.1 and ACVR1 mutations as well as ALT phenotype were only found in WHO grade III-IV astrocytomas, while PIK3CA mutations and PDGFRA gains/amplifications were found in WHO grade II-IV astrocytomas. Approximately 1/3 of DIPG patients had leptomeningeal spread of their tumour. Further, diffuse invasion of the brainstem, spinal cord and thalamus was common with some cases showing spread as distant as the frontal lobes. These findings suggest that focal radiation may be inadequate for some of these patients. Importantly, we show that clinically classic DIPGs represent a diverse histologic spectrum, including multiple cases which would fit WHO criteria of grade II astrocytoma which nevertheless behave clinically as high-grade astrocytomas and harbour the histone K27M-H3.3 mutation. This suggests that the current WHO astrocytoma grading scheme may not appropriately predict outcome for paediatric brainstem gliomas.

Journal Title: Acta neuropathologica

PUBMED ID: 25046485

DOI: doi.org/10.4161/cbt.29926

Titolo: Potential novel role of bevacizumab in glioblastoma and cervical cancer.

Autori: Goey AK., Figg WD.

Data di Pubblicazione: 2014-7-22

Abstract: The VEGF-A binding monoclonal antibody bevacizumab is a widely prescribed angiogenesis inhibitor and indicated for many types of cancer. As shown by three randomized phase 3 trials recently published in the New England Journal of Medicine, novel indications for this drug are still being explored. In the RTOG 0825 and AVAglio trials the effect of bevacizumab addition to standard therapy in newly diagnosed glioblastoma (radiotherapy plus temozolomide) was investigated, while in GOG 240 the combination of platinum-based chemotherapy plus bevacizumab was explored in advanced cervical cancer. In RTOG 0825, addition of bevacizumab to standard therapy did not result in survival benefit, and moreover, quality of life was more deteriorated in the beva-

cizumab arm. In AVAglio, however, progression-free survival (PFS) was significantly increased in the bevacizumab group and these patients also experienced a longer deterioration-free survival. These conflicting results do not fully support the incorporation of bevacizumab in the first-line treatment of glioblastoma. In contrast, in GOG 240 the bevacizumab group (including paclitaxel plus topotecan or paclitaxel) experienced a significant longer PFS and overall survival, and quality of life was not negatively affected in these patients. Thus, these results favor the use of bevacizumab in the treatment of advanced cervical cancer.

Journal Title: Cancer biology & therapy

PUBMED ID: 25038253

DOI: doi.org/10.1093/neuonc/nou129

Titolo: Pseudoprogression in patients with glioblastoma: clinical relevance despite low incidence.

Autori: Radbruch A., Fladt J., Kickingereder P., Wiestler B., Nowosielski M., Bäumer P., Schlemmer HP., Wick A., Heiland S., Wick W., Bendszus M.

Data di Pubblicazione: 2014-7-20

Abstract: This series challenges the current concept of PsP. Even though we could confirm a prolonged OS of patients with PsP, the incidence of PsP was lower than reported previously and extended beyond 12 weeks.

Journal Title: Neuro-oncology

PUBMED ID: 24995786

DOI: doi.org/10.3171/2014.5.JNS132392

Titolo: Phase I/IIa trial of fractionated radiotherapy, temozolomide, and autologous formalin-fixed tumor vaccine for newly diagnosed glioblastoma.

Autori: Ishikawa E., Muragaki Y., Yamamoto T., Maruyama T., Tsuboi K., Ikuta S., Hashimoto K., Uemae Y., Ishihara T., Matsuda M., Matsutani M., Karasawa K., Nakazato Y., Abe T., Ohno T., Matsumura A.

Data di Pubblicazione: 2014-7-5

Abstract: The treatment regimen was well tolerated and resulted in favorable PFS and OS for newly diagnosed GBM patients. Clinical trial registration no.: UMIN000001426 (UMIN clinical trials registry, Japan).

Journal Title: Journal of neurosurgery

PUBMED ID: 24975917

DOI: doi.org/10.1111/1754-9485.12185

Titolo: Hypofractionated intensity-modulated radiotherapy with temozolomide chemotherapy may alter the patterns of failure in patients with glioblastoma multiforme.

Autori: Reddy K., Gaspar LE., Kavanagh BD., Chen C.

Data di Pubblicazione: 2014-7-1

Abstract: A 60-Gy hypo-IMRT treatment delivered in 6-Gy fractions with TMZ altered the patterns of failure in GBM, with more distant failures.

Journal Title: Journal of medical imaging and radiation oncology

PUBMED ID: 24928248

DOI: doi.org/10.1007/s00066-014-0693-2

Titolo: FET-PET-based reirradiation and chloroquine in patients with recurrent glioblastoma: first tolerability and feasibility results.

Autori: Bilger A., Bittner MI., Grosu AL., Wiedenmann N., Meyer PT., Firat E., Niedermann G., Weber WA., Milanović D.

Data di Pubblicazione: 2014-6-15

Abstract: In this case series, we observed encouraging responses to CQ and re-RT. We plan to conduct a CQ dose escalation study combined with re-RT.

Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 24903904

DOI: doi.org/10.1093/neuonc/nou104

Titolo: Survival prediction model of children with diffuse intrinsic pontine glioma based on clinical and radiological criteria.

Autori: Jansen MH., Veldhuijzen van Zanten SE., Sanchez Aliaga E., Heymans M W., Warmuth-Metz M., Hargrave D., van der Hoeven EJ., Gidding CE., de Bont E S., Eshghi OS., Reddingius R., Peeters CM., Schouten-van Meeteren AY., Gooskens RH., Granzen B., Paardekooper GM., Janssens GO., Noske DP., Barkhof F., Kramm CM., Vandertop WP., Kaspers GJ., van Vuurden DG.

Data di Pubblicazione: 2014-6-7

Abstract: We developed a DIPG survival prediction tool that can be used to predict the outcome of patients and for stratification in trials. Validation of the model is needed in a prospective cohort.

Journal Title: Neuro-oncology

PUBMED ID: 24888813

DOI: doi.org/10.1200/JCO.2013.54.0526

Titolo: Antigen-specific immune responses and clinical outcome after vaccination with glioma-associated antigen peptides and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in children with newly diagnosed malignant brainstem and nonbrainstem gliomas.

Autori: Pollack IF., Jakacki RI., Butterfield LH., Hamilton RL., Panigrahy A., Potter DM., Connelly AK., Dibridge SA., Whiteside TL., Okada H.

Data di Pubblicazione: 2014-6-4

Abstract: GAA peptide vaccination in children with gliomas is generally well tolerated and has preliminary evidence of immunologic and clinical responses. Careful monitoring and management of pseudoprogression is essential.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 24882149

DOI: doi.org/10.1016/j.clon.2014.04.001

Titolo: Current concepts in the surgical management of glioma patients.

Autori: Watts C., Price SJ., Santarius T.

Data di Pubblicazione: 2014-6-3

Abstract: The scientific basis for the surgical management of patients with glioma is rapidly evolving. The infiltrative nature of these cancers precludes a surgical cure, but despite this, cytoreductive surgery remains central to high-quality patient care. In addition to tissue sampling for accurate histopathological diagnosis and molecular genetic characterisation, clinical benefit from decompression of space-occupying lesions and microsurgical cytoreduction has been reported in patients with different grades of glioma. By integrating advanced surgical techniques with molecular genetic characterisation of the disease and targeted radiotherapy and chemotherapy, it is possible to construct a programme of personalised surgical therapy throughout the patient journey. The goal of therapeutic packages tailored to each patient is to optimise patient safety and clinical outcome and must be delivered in a multidisciplinary setting. Here we review the current concepts that underlie surgical subspecialisation in the management of patients with glioma.

Journal Title: Clinical oncology (Royal College of Radiologists (Great Britain))

PUBMED ID: 24857153



DOI: doi.org/10.14694/EdBook\_AM.2014.34.e95

Titolo: For the next trick: new discoveries in radiobiology applied to glioblastoma.

Autori: Debus J., Abdollahi A.

Data di Pubblicazione: 2014-5-27

Abstract: Glioblastoma (GBM) is the most common malignant brain tumor. Radiotherapy post surgical resection remained the mainstay of the management of GBM for decades until the addition of temozolomide was shown to prolong the median overall survival (OS) by 2.5 months to 14.6 months in 2005. Infiltrative growth to surrounding normal brain tissue and cooption of vascular niches, peripheral microvascular hyperplasia, and central hypoxic regions with pseudopalisading necrosis are characteristics of GBM and are causally linked to their exceptional radio- and chemo-resistant phenotype. An intratumoral hierarchy is postulated consisting of tumor stem cells in the apex with high DNA-repair proficiency resisting radiotherapy. It is conceivable that the stem cell property is more dynamic than originally anticipated. Niche effects such as exposure to hypoxia and intercellular communication in proximities to endothelial or bone marrow-derived cells (BMDC), for example, may activate such "stem cell" programs. GBM are exceptionally stroma-rich tumors and may consist of more than 70% stroma components, such as microglia and BMDC. It becomes increasingly apparent that treatment of GBM needs to integrate therapies targeting all above-mentioned distinct pathophysiological features. Accordingly, recent approaches in GBM therapy include inhibition of invasion (e.g., integrin, EGFR, CD95, and mTOR inhibition), antiangiogenesis and stroma modulators (TGFbeta, VEGF, angiopoietin, cMET inhibitors) and activation of immune response (vaccination and blockage of negative co-stimulatory signals). In addition, high LET-radiotherapy, for example with carbon ions, is postulated to ablate tumor stem cell and hypoxic cells more efficiently as compared with conventional low-LET photon irradiation. We discuss current key concepts, their limitations, and potentials to improve the outcome in this rapidly progressive and devastating disease.

Journal Title: American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting

PUBMED ID: 24842754

DOI: doi.org/10.1001/jamaneurol.2014.463

Titolo: Effect of rituximab in patients with leucine-rich, glioma-inactivated 1 antibody-associated encephalopathy.

Autori: Irani SR., Gelfand JM., Bettcher BM., Singhal NS., Geschwind MD.

Data di Pubblicazione: 2014-5-21

Abstract: Rituximab was well tolerated in this predominantly older adult patient population and may be an effective option for some patients with LGI1 antibody-associated encephalopathy. Glucocorticoid therapy appears particularly efficacious. Earlier rituximab administration and randomized trials are required to formally assess efficacy.

Journal Title: JAMA neurology

PUBMED ID: 24811110

DOI: doi.org/10.1021/nn5014484

Titolo: A nanoparticle carrying the p53 gene targets tumors including cancer stem cells, sensitizes glioblastoma to chemotherapy and improves survival.

Autori: Kim SS., Rait A., Kim E., Pirollo KF., Nishida M., Farkas N., Dagata JA., Chang EH.

Data di Pubblicazione: 2014-5-10

Abstract: Temozolomide (TMZ)-resistance in glioblastoma multiforme (GBM) has been linked to upregulation of O(6)-methylguanine-DNA methyltransferase (MGMT). Wild-type (wt) p53 was previously shown to down-modulate MGMT. However, p53 therapy for GBM is limited by lack of efficient delivery across the blood

d brain barrier (BBB). We have developed a systemic nanodelivery platform (scL) for tumor-specific targeting (primary and metastatic), which is currently in multiple clinical trials. This self-assembling nanocomplex is formed by simple mixing of the components in a defined order and a specific ratio. Here, we demonstrate that scL crosses the BBB and efficiently targets GBM, as well as cancer stem cells (CSCs), which have been implicated in recurrence and treatment resistance in many human cancers. Moreover, systemic delivery of scL-p53 down-modulates MGMT and induces apoptosis in intracranial GBM xenografts. The combination of scL-p53 and TMZ increased the antitumor efficacy of TMZ with enhanced survival benefit in a mouse model of highly TMZ-resistant GBM. scL-p53 also sensitized both CSCs and bulk tumor cells to TMZ, increasing apoptosis. These results suggest that combining scL-p53 with standard TMZ treatment could be a more effective therapy for GBM.

Journal Title: ACS nano

PUBMED ID: 24809637

DOI: doi.org/10.1016/j.ejrad.2014.03.026

Titolo: Differentiation between vasogenic-edema versus tumor-infiltrative area in patients with glioblastoma during bevacizumab therapy: a longitudinal MRI study.

Autori: Artzi M., Bokstein F., Blumenthal DT., Aizenstein O., Liberman G., Corn BW., Ben Bashat D.

Data di Pubblicazione: 2014-5-10

Abstract: Characterization of non-enhancing hyperintense FLAIR lesion area in GB patients can provide an MR-based biomarker, indicating a shift to an infiltrative progression pattern, and may improve therapy response assessment in patients following bevacizumab therapy.

Journal Title: European journal of radiology

PUBMED ID: 24803676

DOI: doi.org/10.1093/neuonc/nou059

Titolo: Phase II study of sorafenib in children with recurrent or progressive low-grade astrocytomas.

Autori: Karajannis MA., Legault G., Fisher MJ., Milla SS., Cohen KJ., Wisoff JH., Harter DH., Goldberg JD., Hochman T., Merkelson A., Bloom MC., Sievert AJ., Resnick AC., Dhall G., Jones DT., Korshunov A., Pfister SM., Eberhart CG., Zagzag D., Allen JC.

Data di Pubblicazione: 2014-5-8

Abstract: Sorafenib produced unexpected and unprecedented acceleration of tumor growth in children with PLGA, irrespective of NF1 or tumor BRAF status. In vitro studies with sorafenib indicate that this effect is likely related to paradoxical ERK activation. Close monitoring for early tumor progression should be included in trials of novel agents that modulate signal transduction.

Journal Title: Neuro-oncology

PUBMED ID: 24786603

DOI: doi.org/10.1038/bjc.2014.209

Titolo: Phase I study of sorafenib combined with radiation therapy and temozolomide as first-line treatment of high-grade glioma.

Autori: Hottinger AF., Ben Aissa A., Espeli V., Squiban D., Dunkel N., Vargas MI., Hunsberger T., Mach N., Schaller K., Weber DC., Bodmer A., Dietrich PY.

Data di Pubblicazione: 2014-5-3

Abstract: Although Sb can be combined with RT and TMZ, significant side effects and moderate outcome results do not support further clinical development

in malignant gliomas. The robust PK data of the TMZ/Sb combination could be useful in other cancer settings.

Journal Title: British journal of cancer

PUBMED ID: 24768217

DOI: doi.org/10.1016/j.pediatrneurol.2014.02.012

Titolo: Malignant transformation of a desmoplastic infantile ganglioglioma in an infant carrier of a nonsynonymous TP53 mutation.

Autori: Prakash V., Batanian JR., Guzman MA., Duncavage EJ., Geller TJ.

Data di Pubblicazione: 2014-4-29

Abstract: The nonsynonymous variant (p.R248Q in exon 7) of the TP53 gene is predicted to alter the structure of the L2/L3 motif of the DNA binding domain of p53 protein. It was detected in the primary desmoplastic infantile ganglioglioma and glioblastoma multiforme. This child illustrates the rare recurrence of desmoplastic infantile ganglioglioma with malignant transformation to glioblastoma caused by a nonsynonymous TP53 mutation, providing explanation for other rare benign tumor transformations. The TP53 gene is a known primary site of genetic alteration that predisposes to malignant tumors, and this case indicates that it might also be involved in the behavior and outcome of desmoplastic infantile ganglioglioma. Therefore more genetic testing is recommended on desmoplastic infantile ganglioglioma tumors, which may provide biologic prognostic markers.

Journal Title: Pediatric neurology

PUBMED ID: 24758192

DOI: doi.org/10.1186/1748-717X-9-95

Titolo: A comparison of long-term survivors and short-term survivors with glioblastoma, subventricular zone involvement: a predictive factor for survival?

Autori: Adeberg S., Bostel T., König L., Welzel T., Debus J., Combs SE.

Data di Pubblicazione: 2014-4-25

Abstract: Our findings underline that survival in GBM patients is heterogeneous and influenced by multiple factors. This study confirms that tumor location with regard to the SVZ is significantly associated with survival.

Journal Title: Radiation oncology (London, England)

PUBMED ID: 24736829

DOI: doi.org/10.1007/s11060-014-1434-1

Titolo: Clinical management and outcome of histologically verified adult brainstem gliomas in Switzerland: a retrospective analysis of 21 patients.

Autori: Hundsberger T., Tonder M., Hottinger A., Brügge D., Roelcke U., Putora PM., Stupp R., Weller M.

Data di Pubblicazione: 2014-4-17

Abstract: Because of low incidence, mixed study populations and paucity of clinical and histological data, the management of adult brainstem gliomas (BSGs) remains non-standardized. We here describe characteristics, treatment and outcome of patients with exclusively histologically confirmed adult BSGs. A retrospective chart review of adults (age >18 years) was conducted. BSG was defined as a glial tumor located in the midbrain, pons or medulla. Characteristics, management and outcome were analyzed. Twenty one patients (17 male; median age 41 years) were diagnosed between 2004 and 2012 by biopsy (n = 15), partial (n = 4) or complete resection (n = 2). Diagnoses were glioblastoma (WHO grade IV, n = 6), anaplastic astrocytoma (WHO grade III, n = 7), diffuse astrocytoma (WHO grade II, n = 6) and pilocytic astrocytoma (WHO grade I, n = 2). Diffuse gliomas were mainly located in the pons and frequently showed MRI contrast enhancement. Endophytic growth was common (16 vs. 5). Postoperative therapy in low-grade (WHO grade I/II) and high-grade gliomas (WHO

grade III/IV) consisted of radiotherapy alone (three in each group), radiochemotherapy (2 vs. 6), chemotherapy alone (0 vs. 2) or no postoperative therapy (3 vs. 1). Median PFS (24.1 vs. 5.8 months; log-rank,  $p = 0.009$ ) and mOS (30.5 vs. 11.5 months; log-rank,  $p = 0.028$ ) was significantly better in WHO grade II than in WHO grade III/IV tumors. Second-line therapy considerably varied. Histologically verification of adult BSGs is feasible and has an impact on postoperative treatment. Low-grade gliomas can simply be followed or treated with radiotherapy alone. Radiochemotherapy with temozolomide can safely be prescribed for high-grade gliomas without additional CNS toxicities.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 24732058

DOI: doi.org/10.1097/MPH.0000000000000162

Titolo: Inadvertent high-dose therapy with temozolomide in a child with recurrent pontine glioma followed by a rapid clinical response but deteriorated after substitution with low-dose therapy.

Autori: Wang ZJ., Altonok D., Sood S., Konski A., Poulik J.

Data di Pubblicazione: 2014-4-16

Abstract: We present a case of inadvertent high-dose therapy with temozolomide in a child with recurrent diffuse intrinsic pontine glioma followed by a rapid clinical response. The patient was a 7-year-old boy who initially presented with a history of left facial palsy, double vision, headache, and ataxia. His symptoms were completely resolved following radiotherapy but recurred 3 months after. Following recurrence, he received temozolomide in a dose > 3 times higher than prescribed inadvertently but tolerated well with a rapid clinical response. He eventually deteriorated after he was substituted with a lower dose of temozolomide and died.

Journal Title: Journal of pediatric hematology/oncology

PUBMED ID: 24729041

DOI: doi.org/10.1093/ndt/gfu013

Titolo: The effect of everolimus on renal angiomyolipoma in patients with tuberous sclerosis complex being treated for subependymal giant cell astrocytoma: subgroup results from the randomized, placebo-controlled, Phase 3 trial EXIST-1.

Autori: Kingswood JC., Jozwiak S., Belousova ED., Frost MD., Kuperman RA., Bebin EM., Korf BR., Flamini JR., Kohrman MH., Sparagana SP., Wu JY., Brechenmacher T., Stein K., Berkowitz N., Bissler JJ., Franz DN.

Data di Pubblicazione: 2014-4-15

Abstract: Everolimus showed efficacy in reducing angiomyolipoma lesion volume in patients with SEGA associated with TSC. The trial is registered with ClinicalTrials.gov, number NCT00789828; <http://clinicaltrials.gov/ct2/show/NCT00789828?term=EXIST-1&rank=1>.

Journal Title: Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association

PUBMED ID: 24728785

DOI: doi.org/10.1007/s11060-013-1337-6

Titolo: The role of radiotherapy in the management of progressive glioblastoma : a systematic review and evidence-based clinical practice guideline.

Autori: Ryu S., Buatti JM., Morris A., Kalkanis SN., Ryken TC., Olson JJ., Olson JJ.

Data di Pubblicazione: 2014-4-15

Abstract: Re-irradiation is recommended in order to maintain or improve a patient's neurological status and quality of life prior to any further tumor progression.

Journal Title: Journal of neuro-oncology

PUBMED ID: 24727314

DOI: doi.org/10.1212/WNL.0000000000000402

Titolo: Progression types after antiangiogenic therapy are related to outcome in recurrent glioblastoma.

Autori: Nowosielski M., Wiestler B., Goebel G., Hutterer M., Schlemmer HP., Stockhammer G., Wick W., Bendszus M., Radbruch A.

Data di Pubblicazione: 2014-4-15

Abstract: Radiologic PTs following bevacizumab treatment failure show differences in time to development and are related to outcome. We therefore hypothesize that these PTs reflect a different glioma biology, including differential resistance mechanisms to bevacizumab, and may be associated with different responses to postprogression therapy.

Journal Title: Neurology

PUBMED ID: 24725538

DOI: doi.org/10.1186/1471-2407-14-258

Titolo: Complete clinical regression of a BRAF V600E-mutant pediatric glioblastoma multiforme after BRAF inhibitor therapy.

Autori: Robinson GW., Orr BA., Gajjar A.

Data di Pubblicazione: 2014-4-15

Abstract: This is the first report of a complete response of relapsed glioblastoma multiforme to targeted BRAF inhibitor therapy. While not a predominant mutation in glioblastoma multiforme, the increased prevalence of BRAF V600 mutations in pediatric CNS tumors and certain subtypes marks a population to whom this therapy could be applied. Response to this therapy suggests that BRAF inhibitors can affect primary CNS lesions when a documented and targetable mutation is present.

Journal Title: BMC cancer

PUBMED ID: 24724714

DOI: doi.org/10.3171/2014.3.PEDS13455

Titolo: Clinical course of vestibular schwannoma in pediatric neurofibromatosis Type 2.

Autori: Choi JW., Lee JY., Phi JH., Wang KC., Chung HT., Paek SH., Kim DG., Park SH., Kim SK.

Data di Pubblicazione: 2014-4-15

Abstract: Clinical manifestations in children with NF2 were highly variable, compared with their adult counterparts. The natural growth rate of VS in children is slow, and this oncological feature may explain the diverse clinical manifestations besides vestibular symptoms in children with NF2. The treatment outcome of GKS for VS in children with NF2 was not favorable compared with previous reports of affected adults.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 24723564

DOI: doi.org/10.1093/neuonc/nou045

Titolo: Significance of interleukin-13 receptor alpha 2-targeted glioblastoma therapy.

Autori: Thaci B., Brown CE., Binello E., Werbaneth K., Sampath P., Sengupta S.

Data di Pubblicazione: 2014-4-12

Abstract: Glioblastoma multiforme (GBM) remains one of the most lethal primary brain tumors despite surgical and therapeutic advancements. Targeted therapies of neoplastic diseases, including GBM, have received a great deal of i

interest in recent years. A highly studied target of GBM is interleukin-13 receptor  $\alpha$  chain variant 2 (IL13R $\alpha$ 2). Targeted therapies against IL13R $\alpha$ 2 in GBM include fusion chimera proteins of IL-13 and bacterial toxins, nanoparticles, and oncolytic viruses. In addition, immunotherapies have been developed using monoclonal antibodies and cell-based strategies such as IL13R $\alpha$ 2-pulsed dendritic cells and IL13R $\alpha$ 2-targeted chimeric antigen receptor-modified T cells. Advanced therapeutic development has led to the completion of phase I clinical trials for chimeric antigen receptor-modified T cells and phase III clinical trials for IL-13-conjugated bacterial toxin, with promising outcomes. Selective expression of IL13R $\alpha$ 2 on tumor cells, while absent in the surrounding normal brain tissue, has motivated continued study of IL13R $\alpha$ 2 as an important candidate for targeted glioma therapy. Here, we review the preclinical and clinical studies targeting IL13R $\alpha$ 2 in GBM and discuss new advances and promising applications.

Journal Title: Neuro-oncology

PUBMED ID: 24723487

DOI: doi.org/10.1093/annonc/mdu148

Titolo: Randomized phase II trial of irinotecan and bevacizumab as neo-adjuvant and adjuvant to temozolomide-based chemoradiation compared with temozolomide-chemoradiation for unresectable glioblastoma: final results of the TEMA VIR study from ANOCEF+.

Autori: Chauffert B., Feuvret L., Bonnetain F., Taillandier L., Frappaz D., Taillia H., Schott R., Honnorat J., Fabbro M., Tennevet I., Ghiringhelli F., Guillermo JS., Durando X., Castera D., Frenay M., Campello C., Dalban C., Skrzypski J., Chinot O.

Data di Pubblicazione: 2014-4-12

Abstract: Clinical trial registered under EUDRACT number 2008-002775-28 (NCT 01022918).

Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 24696052

DOI: doi.org/10.1007/s11060-014-1428-z

Titolo: Results of nimotuzumab and vinorelbine, radiation and re-irradiation for diffuse pontine glioma in childhood.

Autori: Massimino M., Biassoni V., Miceli R., Schiavello E., Warmuth-Metz M., Modena P., Casanova M., Pecori E., Giangaspero F., Antonelli M., Buttarelli FR., Potepan P., Pollo B., Nunziata R., Spreafico F., Podda M., Anichini A., Clerici CA., Sardi I., De Cecco L., Bode U., Bach F., Gandola L.

Data di Pubblicazione: 2014-4-4

Abstract: Radiotherapy is the only treatment definitely indicated for diffuse pontine gliomas (DIPG). Findings on the role of EGFR signaling in the onset of childhood DIPG prompted the use of nimotuzumab, an anti-EGFR monoclonal antibody. Assuming a potential synergy with both radiotherapy and vinorelbine, a pilot phase 2 protocol was launched that combined nimotuzumab with concomitant radiation and vinorelbine. An amendment in July 2011 introduced re-irradiation at relapse. The primary endpoint for first-line treatment was objective response rate (CR + PR + SD) according to the RECIST. This report concerns the outcome of this strategy as a whole. Vinorelbine 20 mg/m<sup>2</sup> was administered weekly, with nimotuzumab 150 mg/m<sup>2</sup> in the first 12 weeks of treatment; radiotherapy was delivered from weeks 3 to 9, for a total dose of 54 Gy. Vinorelbine 25 mg/m<sup>2</sup> and nimotuzumab were given every other week thereafter until the tumor progressed or for up to 2 years. Re-irradiation consisted of 19.8 Gy, fractionated over 11 days. Baseline and latest MRIs were assessed blindly by an outside neuroradiologist. Twenty five children (mean age 7.4 years) were enrolled as of August 2009 (median follow-up 29 months). A response was observed in 24/25 patients (96 %). The nimotuzumab/vinorelbine c

ombination was very well tolerated, with no acute side-effects. Eleven of 16 locally-relapsing patients were re-irradiated. One-year PFS and OS rates were  $30 \pm 10 \%$  and  $76 \pm 9 \%$ , respectively; 2-year OS was  $27 \pm 9 \%$ ; the median PFS and OS were 8.5 and 15 months, respectively. This strategy generated interesting results and warrants further investigation.

Journal Title: Journal of neuro-oncology

PUBMED ID: 24661654

DOI: doi.org/10.1016/j.ijrobp.2014.01.013

Titolo: Postponed is not canceled: role of craniospinal radiation therapy in the management of recurrent infant medulloblastoma--an experience from the HIT-REZ 1997 & 2005 studies.

Autori: Müller K., Mynarek M., Zwiener I., Siegler N., Zimmermann M., Christiansen H., Budach W., Henke G., Warmuth-Metz M., Pietsch T., von Hoff K., von Bueren A., Bode U., Rutkowski S., Kortmann RD., Fleischhack G., Tippelt S.  
Data di Pubblicazione: 2014-3-26

Abstract: Our results suggest that salvage treatment of relapsed medulloblastomas consisting of CSI and chemotherapy offers a second chance for cure, even for patients with classic histological findings. Metastatic disease at relapse did not have an impact on survival. However, this may be explained by the small number of patients.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 24652192

DOI: doi.org/10.1007/s12032-014-0924-5

Titolo: STAT3 Tyr705 phosphorylation affects clinical outcome in patients with newly diagnosed supratentorial glioblastoma.

Autori: Lin GS., Yang LJ., Wang XF., Chen YP., Tang WL., Chen L., Lin ZX.  
Data di Pubblicazione: 2014-3-22

Abstract: STAT3 tyrosine705 phosphorylation (p-STAT3, Tyr705), a molecular hub for several signal transduction pathways of glioma, plays a central role in glioblastoma (GBM) carcinogenesis and progression. However, it is still controversial whether p-STAT3 expression is associated with the clinical outcome of patients with glioblastoma. Such evidence would contribute to further illustrate whether STAT3 inhibition is suitable for clinical treatment. Here, we examined the expression of p-STAT3 in the tumor tissues from 90 patients with newly diagnosed supratentorial GBM via immunohistochemical technique and evaluated the influences of its expression on progression-free survival (PFS) and overall survival (OS) using the Kaplan-Meier curve and COX proportional hazards regression model. Immunohistochemical assay indicated increased expression of p-STAT3 in GBM tissue compared to adjacent normal brain tissue without p-STAT3 expression. There were no observed associations between p-STAT3 expression and patients' gender ( $P = 0.660$ ), age ( $P = 0.867$ ) or preoperative Karnofsky Performance Status (KPS) ( $P = 0.121$ ). Univariate survival analysis revealed significant correlations of high p-STAT3 expression with shorter PFS ( $P = 0.012$ ) and OS ( $P = 0.009$ ). Multivariate survival analysis confirmed high p-STAT3 expression as a significant prognostic indicator for shorter PFS (HR 2.158,  $P = 0.019$ ) and OS (HR 2.120,  $P = 0.031$ ), independent of age, KPS and chemoradiotherapy. In summary, the high percentage of p-STAT3 positive tumor cells is a significant independent prognostic indicator for poor clinical outcome in patients with GBM, in addition to advanced age, poor performance status and nonstandard chemoradiotherapy, suggesting that STAT3 might be as a promising therapeutic target in GBM.

Journal Title: Medical oncology (Northwood, London, England)

PUBMED ID: 24637230

DOI: doi.org/10.1093/neuonc/nou029

Titolo: A single-institution phase II trial of radiation, temozolomide, erlotinib, and bevacizumab for initial treatment of glioblastoma.

Autori: Clarke JL., Molinaro AM., Phillips JJ., Butowski NA., Chang SM., Perry A., Costello JF., DeSilva AA., Rabbitt JE., Prados MD.

Data di Pubblicazione: 2014-3-19

Abstract: The combination of bevacizumab, erlotinib, TMZ, and radiotherapy appears to be well tolerated and improved progression-free survival but did not reach the primary endpoint of improved OS.

Journal Title: Neuro-oncology

PUBMED ID: 24616497

DOI: doi.org/10.1073/pnas.1323855111

Titolo: In vivo chemical exchange saturation transfer imaging allows early detection of a therapeutic response in glioblastoma.

Autori: Sagiya K., Mashimo T., Togao O., Vemireddy V., Hatanpaa KJ., Maher EA., Mickey BE., Pan E., Sherry AD., Bachoo RM., Takahashi M.

Data di Pubblicazione: 2014-3-12

Abstract: Glioblastoma multiforme (GBM), which accounts for more than 50% of all gliomas, is among the deadliest of all human cancers. Given the dismal prognosis of GBM, it would be advantageous to identify early biomarkers of a response to therapy to avoid continuing ineffective treatments and to initiate other therapeutic strategies. The present in vivo longitudinal study in an orthotopic mouse model demonstrates quantitative assessment of early treatment response during short-term chemotherapy with temozolomide (TMZ) by amide proton transfer (APT) imaging. In a GBM line, only one course of TMZ (3 d exposure and 4 d rest) at a dose of 80 mg/kg resulted in substantial reduction in APT signal compared with untreated control animals, in which the APT signal continued to increase. Although there were no detectable differences in tumor volume, cell density, or apoptosis rate between groups, levels of Ki67 (index of cell proliferation) were substantially reduced in treated tumors. In another TMZ-resistant GBM line, the APT signal and levels of Ki67 increased despite the same course of TMZ treatment. As metabolite changes are known to occur early in the time course of chemotherapy and precede morphologic changes, these results suggest that the APT signal in glioma may be a useful functional biomarker of treatment response or degree of tumor progression. Thus, APT imaging may serve as a sensitive biomarker of early treatment response and could potentially replace invasive biopsies to provide a definitive diagnosis. This would have a major impact on the clinical management of patients with glioma.

Journal Title: Proceedings of the National Academy of Sciences of the United States of America

PUBMED ID: 24608453

DOI: doi.org/10.4103/0028-3886.128280

Titolo: Sulfasalazine and temozolomide with radiation therapy for newly diagnosed glioblastoma.

Autori: Takeuchi S., Wada K., Nagatani K., Otani N., Osada H., Nawashiro H.

Data di Pubblicazione: 2014-3-11

Abstract: Sulfasalazine treatment with temozolomide plus radiotherapy for newly diagnosed primary GBM is associated with a high rate of discontinuation due to hematologic toxic effects. This treatment may have no effect on OS or PFS, although it may improve seizure control if an adequate dose can be administered.

Journal Title: Neurology India

PUBMED ID: 24604590

DOI: doi.org/10.1007/s00259-013-2678-2



Titolo:  $^{18}\text{F}$ -FLT and  $^{18}\text{F}$ -FDOPA PET kinetics in recurrent brain tumors.

Autori: Wardak M., Schiepers C., Cloughesy TF., Dahlbom M., Phelps ME., Huang SC.

Data di Pubblicazione: 2014-3-8

Abstract: For recurrent malignant glioma treated with bevacizumab and irinotecan, FLT kinetic parameters obtained early after the start of treatment (absolute values and their associated changes) can provide sufficient information to predict OS with reasonable confidence using MLR. The slight increase in accuracy for predicting OS with a combination of FLT and FDOPA PET information may not warrant the additional acquisition of FDOPA PET for therapy monitoring in patients with recurrent glioma.

Journal Title: European journal of nuclear medicine and molecular imaging

PUBMED ID: 24560760

DOI: doi.org/10.1016/j.radonc.2014.01.013

Titolo: Hypofractionated conformal radiotherapy for pediatric diffuse intrinsic pontine glioma (DIPG): a randomized controlled trial.

Autori: Zaghloul MS., Eldebawy E., Ahmed S., Mousa AG., Amin A., Refaat A., Zaky I., Elkhateeb N., Sabry M.

Data di Pubblicazione: 2014-2-25

Abstract: Hypofractionated radiotherapy offers lesser burden on the patients, their families and the treating departments, with nearly comparable results to conventional fractionation, though not fulfilling the non-inferiority assumption.

Journal Title: Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology

PUBMED ID: 24498562

DOI: doi.org/10.4161/onci.26968

Titolo: CSF1R inhibition delays cervical and mammary tumor growth in murine models by attenuating the turnover of tumor-associated macrophages and enhancing infiltration by CD8

Autori: Strachan DC., Ruffell B., Oei Y., Bissell MJ., Coussens LM., Pryer N., Daniel D.

Data di Pubblicazione: 2014-2-6

Abstract: Increased numbers of tumor-infiltrating macrophages correlate with poor disease outcome in patients affected by several types of cancer, including breast and prostate carcinomas. The colony stimulating factor 1 receptor (CSF1R) signaling pathway drives the recruitment of tumor-associated macrophages (TAMs) to the neoplastic microenvironment and promotes the differentiation of TAMs toward a pro-tumorigenic phenotype. Twelve clinical trials are currently evaluating agents that target the CSF1/CSF1R signaling pathway as a treatment against multiple malignancies, including breast carcinoma, leukemia, and glioblastoma. The blockade of CSF1R signaling has been shown to greatly decrease the number of macrophages in a tissue-specific manner. However, additional mechanistic insights are needed in order to understand how macrophages are depleted and the global effects of CSF1R inhibition on other tumor-infiltrating immune cells. Using BLZ945, a highly selective small molecule inhibitor of CSF1R, we show that CSF1R inhibition attenuates the turnover rate of TAMs while increasing the number of CD8

Journal Title: Oncoimmunology

PUBMED ID: 24482196

DOI: doi.org/10.1002/pbc.24971

Titolo: Effect of time from diagnosis to start of radiotherapy on children with diffuse intrinsic pontine glioma.

Autori: Pai Panandiker AS., Wong JK., Nedelka MA., Wu S., Gajjar A., Broniscer A.

Data di Pubblicazione: 2014-2-1

Abstract: Time as a continuous variable did not affect OS or EFS in our cohort; however, children treated within 2 weeks of diagnosis had poor outcomes. Although rapid initiation of RT is desirable, our findings do not support intensive efforts aimed at shortening delays from diagnosis to start of RT.

Journal Title: Pediatric blood & cancer

PUBMED ID: 24477622

DOI: doi.org/10.1007/s11060-014-1374-9

Titolo: Prognostic significance of telomere maintenance mechanisms in pediatric high-grade gliomas.

Autori: Dorris K., Sobo M., Onar-Thomas A., Panditharatna E., Stevenson CB., Gardner SL., Dewire MD., Pierson CR., Olshefski R., Rempel SA., Goldman S., Miles L., Fouladi M., Drissi R.

Data di Pubblicazione: 2014-1-31

Abstract: Children with high-grade glioma, including diffuse intrinsic pontine glioma (DIPG), have a poor prognosis despite multimodal therapy. Identifying novel therapeutic targets is critical to improve their outcome. We evaluated prognostic roles of telomere maintenance mechanisms in children with HGG, including DIPG. A multi-institutional retrospective study was conducted involving 50 flash-frozen HGG (35 non-brainstem; 15 DIPG) tumors from 45 children (30 non-brainstem; 15 DIPG). Telomerase activity, expression of hTERT mRNA (encoding telomerase catalytic component) and TERC (telomerase RNA template) and alternative lengthening of telomeres (ALT) mechanism were assayed. Cox Proportional Hazard regression analyses assessed association of clinical and pathological variables, TERC and hTERT levels, telomerase activity, and ALT use with progression-free or overall survival (OS). High TERC and hTERT expression was detected in 13/28 non-brainstem HGG samples as compared to non-neoplastic controls. High TERC and hTERT expression was identified in 13/15 and 11/15 DIPG samples, respectively, compared to controls. Evidence of ALT was noted in 3/11 DIPG and 10/19 non-brainstem HGG specimens. ALT and telomerase use were identified in 4/19 non-brainstem HGG and 2/11 DIPG specimens. In multivariable analyses, increased TERC and hTERT levels were associated with worse OS in patients with non-brainstem HGG, after controlling for tumor grade or resection extent. Children with HGG and DIPG, have increased hTERT and TERC expression. In children with non-brainstem HGG, increased TERC and hTERT expression levels are associated with a worse OS, making telomerase a promising potential therapeutic target in pediatric HGG.

Journal Title: Journal of neuro-oncology

PUBMED ID: 24469854

DOI: doi.org/10.1007/s11060-014-1366-9

Titolo: Factors impacting survival following second surgery in patients with glioblastoma in the temozolomide treatment era, incorporating neutrophil/lymphocyte ratio and time to first progression.

Autori: McNamara MG., Lwin Z., Jiang H., Templeton AJ., Zadeh G., Bernstein M., Chung C., Millar BA., Laperriere N., Mason WP.

Data di Pubblicazione: 2014-1-29

Abstract: Patients with progressive glioblastoma (GBM) have a poor prognosis. Neutrophil/lymphocyte ratio (NLR), a host inflammatory marker, is prognostic in several solid tumors. The prognostic impact of either NLR, or time from first surgery for GBM to first progression (TTP), in patients undergoing second surgery, has not been assessed. Patients undergoing second surgery for GBM were retrospectively reviewed. Primary outcome was overall survival (OS) and Cox proportional hazard models were used to assess the prognostic value of baseline characteristics including TTP and NLR. Univariable and multivariable

able analysis (MVA) of OS from second surgery were performed using accelerated failure time Weibull model. Of 584 patients with GBM, 107 (18 %) underwent second surgery between 01/04 and 12/11. Patients who underwent second surgery had longer OS versus those having primary surgery alone; 20.9 versus 9.9 months ( $P < 0.001$ ). Median OS from second surgery in patients with  $NLR \leq 4$  versus  $NLR > 4$  was 9.7 versus 5.9 months (log rank  $P = 0.02$ ). The NLR retained its prognostic significance for survival on MVA (time ratio [TR] 1.65, 95 % confidence interval [CI] 1.15-2.35,  $P < 0.01$ ). No chemotherapy post second surgery (TR 0.23, 95 % CI 0.16-0.33,  $P < 0.001$ ) portended worse survival. In patients undergoing second surgery, when TTP was  $\leq 12$  months, 12-24 months, or  $>24$  months, median OS from second surgery was 7.2, 7.0 and 6.3 months, respectively ( $P = 0.6$ ). A  $NLR > 4$  prior to second surgery is a poor prognostic factor in GBM and later progression is associated with longer survival in patients but not in longer survival after second surgery.

Journal Title: Journal of neuro-oncology

PUBMED ID: 24441743

DOI: doi.org/10.1097/CAD.0000000000000077

Titolo: Sorafenib for patients with pretreated recurrent or progressive high-grade glioma: a retrospective, single-institution study.

Autori: Hassler MR., Ackerl M., Flechl B., Sax C., Wöhrer A., Widhalm G., Dieckmann K., Hainfellner J., Preusser M., Marosi C.

Data di Pubblicazione: 2014-1-21

Abstract: Therapeutic options for patients with pretreated advanced high-grade glioma (HGG) are limited. Sorafenib, a small molecule with multiple potential beneficial actions, appears particularly promising. We reviewed the outcomes of 30 patients with recurrent or progressive HGG treated with sorafenib within a named patient program. Overall, 16 patients suffered from recurrent or progressive glioblastoma multiforme and 14 patients had grade 3 gliomas. All but four patients had previously undergone surgical debulking; all but one patient had received previous standard multimodal treatment; and 18 patients (60%) had received more than one line of chemotherapy, in median three. Progression-free survival (PFS), defined as the time from initiation of sorafenib to treatment discontinuation because of tumor progression or death, was selected as the endpoint. The use of sorafenib resulted in a median PFS of 3 months [95% confidence interval (CI) 1.9-4.1 months] in patients with glioblastoma and of 3.1 months (95% CI 1.4-4.8 months) in patients with other HGG. The PFS-6 for the whole cohort was 23%. Sixteen patients reported adverse events, mostly moderate, with hypertension as the most frequently reported toxicity (seven patients). One patient died of cerebral bleeding (grade 5 toxicity). The overall survival after initiation of sorafenib was 6 months (95% CI 3.9-8.0 months) for patients with glioblastoma multiforme and 10 months (95% CI 3.1-16.9 months) for patients with HGG. In this retrospective analysis of heavily pretreated patients with HGG, sorafenib monotherapy was associated with tumor stabilization in a small subset of patients. The risk-benefit ratio was acceptable in the context of an apparent clinical benefit in patients with a fatal disease.

Journal Title: Anti-cancer drugs

PUBMED ID: 24429479

DOI: doi.org/10.1007/s00066-013-0506-z

Titolo: Low-dose fractionated radiotherapy and concomitant chemotherapy for recurrent or progressive glioblastoma: final report of a pilot study.

Autori: Balducci M., Diletto B., Chiesa S., D'Agostino GR., Gambacorta MA., Ferro M., Colosimo C., Maira G., Anile C., Valentini V.

Data di Pubblicazione: 2014-1-17

Abstract: LD-FRT and chemotherapy for recurrent/progressive GBM have a good toxicity profile and clinical outcomes, even though further investigation of this novel palliative treatment approach is warranted.

Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 24420674

DOI: doi.org/10.1007/s00381-014-2359-x

Titolo: Diffuse intrinsic pontine glioma in children and adolescents: a single-center experience.

Autori: Vallero SG., Bertin D., Basso ME., Pittana LS., Mussano A., Fagioli F.

Data di Pubblicazione: 2014-1-15

Abstract: Radiotherapy followed by VCR or TMZ allows obtaining results that are in line with previous reports, with no advantages over other similar treatment schedules. DIPGs are challenging tumors with a dismal outcome. Further research and newer therapies are urgently needed in order to achieve improvements in survival.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 24410308

DOI: doi.org/10.2174/1574886308666140106154343

Titolo: A fatal case of acute interstitial pneumonia (AIP) in a woman affected by glioblastoma.

Autori: Balzarini L., Mancini C., Marvisi M.

Data di Pubblicazione: 2014-1-14

Abstract: This report presents the case of a 67-year-old woman affected by glioblastoma. After a few days of adjuvant therapy with temozolomide and prophylaxis with trimetoprim-sulfamethoxazole to prevent Pneumocystis Jiroveci, she had progressive and rapid worsening of symptoms with weakness, dyspnea and orthopnea. She had peripheral edema and proximal hyposthenia of the lower limbs. Chest CT showed bilateral ground-glass opacities and laboratory exams revealed hypoxemia and hypocapnia, an initial reduction in platelet and white blood cells, and an elevation of LDH, AST, ALT, and active urinary sediment. Blood cultures, bronchoalveolar lavage (BAL) data and transbronchial biopsy showed no infections, and in particular no evidence of Pneumocystis Jiroveci pneumonia. Histological examination revealed a typical pattern of AIP. She was treated with broad-spectrum antibiotics and high-dose steroids. The symptoms worsened and respiratory failure required mechanical ventilation. The pneumonia was not responsive to medical or invasive care. She died after ten days of hospitalization. At present very little can be found in the literature about lung toxicity caused by temozolomide. This case can be added as a new report describing this risk. The combination therapy with temozolomide and trimetoprim-sulfamethoxazole could have a synergistic action inducing various forms of pulmonary toxicity. ESTABLISHED FACTS: Acute interstitial pneumonia is a common manifestation of lung toxicity caused by drugs. The clinical course is favorable with a good response to corticosteroids. NOVEL INSIGHT: This is the first fatal case of lung toxicity caused by Temozolomide. Clinicians must be aware that a combination therapy including trimetoprim-sulfamethoxazole could have a synergistic action in inducing pulmonary toxicity.

Journal Title: Current drug safety

PUBMED ID: 24403482

DOI: Mancante

Titolo: Survival and prognostic factors in children with brain tumors: long-term follow-up single center study in Poland.

Autori: Pogorzala M., Styczynski J., Wysocki M.

Data di Pubblicazione: 2014-1-10

Abstract: Long-term survival was achieved by 58% of children with brain tumors. Advanced tumor stage, incomplete surgical resection, complications of surgical treatment, and progression of the disease during treatment predicted poor outcome.

Journal Title: Anticancer research

PUBMED ID: 24403268

DOI: doi.org/10.1002/cam4.154

Titolo: Efficacy of salvage stereotactic radiotherapy for recurrent glioma: impact of tumor morphology and method of target delineation on local control

Autori: Ogura K., Mizowaki T., Arakawa Y., Sakanaka K., Miyamoto S., Hiraoka M.

Data di Pubblicazione: 2014-1-10

Abstract: In this study, we assessed the efficacy of salvage stereotactic radiotherapy (SRT) for recurrent glioma. From August 2008 to December 2012, 30 patients with recurrent glioma underwent salvage SRT. The initial histologic diagnoses were World Health Organization (WHO) grades II, III, and IV in 6, 9, and 15 patients, respectively. Morphologically, the type of recurrence was classified as diffuse or other. Two methods of clinical target delineation were used: A, a contrast-enhancing tumor; or B, a contrast-enhancing tumor with a 3-10-mm margin and/or surrounding fluid attenuation inversion recovery (FLAIR) high-intensity areas. The prescribed dose was 22.5-35 Gy delivered in five fractions at an isocenter using a dynamic conformal arc technique. The overall survival (OS) and local control probability (LCP) after SRT were calculated using the Kaplan-Meier method. A univariate analysis was used to test the effect of clinical variables on OS/LCP. The median follow-up period was 272 days after SRT. The OS and LCP were 83% and 56% at 6 months after SRT, respectively. Morphologically, the tumor type correlated significantly with both OS and LCP ( $P = 0.006$  and  $<0.001$ , respectively). The method of target delineation also had a significant influence on LCP ( $P = 0.016$ ). Grade 3 radiation necrosis was observed in two patients according to Common Terminology Criteria for Adverse Events, version 3. Salvage SRT was safe and effective for recurrent glioma, especially non-diffuse recurrences. Improved local control might be obtained by adding a margin to contrast-enhancing tumors or including increased FLAIR high-intensity areas.

Journal Title: Cancer medicine

PUBMED ID: 24395350

DOI: doi.org/10.1007/s11060-013-1352-7

Titolo: Neoadjuvant cisplatin plus temozolomide versus standard treatment in patients with unresectable glioblastoma or anaplastic astrocytoma: a differential effect of MGMT methylation.

Autori: Capdevila L., Cros S., Ramirez JL., Sanz C., Carrato C., Romeo M., Etzaniz O., Hostalot C., Massuet A., Cuadra JL., Villà S., Balaña C.

Data di Pubblicazione: 2014-1-8

Abstract: Patients with unresectable glioblastoma or anaplastic astrocytoma have a dismal prognosis. The role of neoadjuvant chemotherapy prior to irradiation in these patients has been studied primarily in non-randomized studies. We have compared the effect of neoadjuvant chemotherapy plus radiotherapy versus concomitant radiotherapy plus temozolomide in a retrospective analysis of two consecutive series of patients in whom surgery consisted of biopsy only. From 2003 to 2005, 23 patients received two cycles of temozolomide plus cisplatin followed by radiotherapy (Cohort 1), and from 2006 to 2010, 23 additional patients received concomitant radiotherapy and temozolomide followed by adjuvant temozolomide (Cohort 2). In Cohort 1, 91.3 % of patients rece

ived all planned chemotherapy cycles. Progression-free and overall survival were 3.3 and 8.5 months, respectively. In Cohort 2, progression-free and overall survival were 5.1 and 11.2 months, respectively. No differences between the two groups were observed in rate of completion of radiotherapy, progression-free or overall survival. MGMT methylation was assessed in 91.3 % of patients. In Cohort 1, patients without MGMT methylation showed a trend towards shorter progression-free survival ( $P = 0.09$ ), while in Cohort 2, patients without MGMT methylation had longer progression-free survival ( $P = 0.04$ ). In the overall patient population, neoadjuvant temozolomide plus cisplatin had neither a positive nor negative influence on outcome. However, our findings indicate that patients with methylated MGMT may derive greater benefit from neoadjuvant temozolomide than those with unmethylated MGMT.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 24390814

DOI: doi.org/10.1007/s11940-013-0273-2

Titolo: Gliomatosis cerebri: a review.

Autori: Rudà R., Bertero L., Sanson M.

Data di Pubblicazione: 2014-1-7

Abstract: Gliomatosis cerebri (GC) is an intriguing disease for several reasons. First, it is difficult to draw the border between GC and diffuse gliomas. In this regard, GC could represent the most invasive form of diffuse gliomas. Second, both in terms of histologic grading and clinical course, GC is a heterogeneous disease, ranging from rapidly evolving to slowly and somewhat indolent forms. Because of the extensive spread of the disease, surgery outside a biopsy for diagnosis is rarely indicated in gliomatosis cerebri. The therapeutic options include radiotherapy, generally involving the whole brain, and chemotherapy with temozolomide or nitrosoureas. Because of the rarity of the disease, no trial comparing these two modalities has been undertaken so far. Decision is, therefore, based on small retrospective noncomparative studies and expert opinions. On one hand, there is a rationale to postpone the whole brain radiotherapy because of late neurotoxicity, but on the other hand, there is also the risk that an aggressive disease evolves to intracranial hypertension making the radiotherapy hazardous or even impossible. As a consequence, the patient would lose the opportunity to receive a potentially effective treatment. In this decision, the evaluation of histologic data together with clinical and radiologic features, performance status, and molecular profile may be of help. Because radiotherapy usually involves large volumes of the brain, chemotherapy is generally preferred up front in patients with a slowly evolving disease. Conversely, in patients with rapidly (ie, over few weeks) evolving disease with neurologic deficits or when histologic features of glioblastoma are evident, whole brain radiotherapy (45 Gy with 1.8 Gy fractions), alone or associated with concomitant temozolomide, is often preferred. The value of advanced of magnetic resonance imaging and positron emission tomography techniques to predict outcome and monitoring the treatment still remains to be defined.

Journal Title: Current treatment options in neurology

PUBMED ID: 24353988

DOI: doi.org/MagyOnkol.2013.57.4.232

Titolo: [Results of postoperative radiochemotherapy of glioblastoma multiforme].

Autori: Lövey J., Fedorcsák I., Bajcsay A., Sipos L., Mangel L., Kásler M., Bagó A.

Data di Pubblicazione: 2013-12-20

Abstract: Glioblastoma multiforme has one of the worst prognoses of all cancers. A substantial progression in its treatment has been achieved only eight years ago when a new adjuvant radiochemotherapy regimen containing temozolom

id has been introduced to the clinical practice. In this paper we evaluate the treatment results in adjuvant radiochemotherapy of glioblastoma carried out by two neurosurgery and oncology centers in Budapest, Hungary and we compared our results to the data of the reference phase III registration trial of the EORTC/NCIC. We analyzed the data of 210 patients treated for glioblastoma between 2005 and 2013. The primary endpoints of our study were overall survival and side effects. We studied and statistically analyzed the influence of multiple factors on survival. We compared our results with the data of the reference study and other results published in the literature. The median follow-up for the surviving patients in our study was 52 months. The median age of our patients was 58 (18-79) years. Seventy-two women and 138 men have been treated. The median overall survival was 17 (3-96) months, the progression-free survival 11 (3-96) months. The radiochemotherapy phase was completed in 95.2% and the monotherapy phase in 68% of all cases. Univariate analysis showed that age, ECOG status and RPA class had significant influence on survival. In multivariate analysis only RPA class remained statistically significant (RR 1.86, 95% CI 1.14-3.05). The proportion of grade III and worse side effects during the chemoradiation phase was 3.8% and in the monotherapy phase 1.9%. These were hematological side effects only. Serious hematological sequelae occurred nearly exclusively in women. Comparing to the reference study the demographic distribution of the patients was similar in our study but among our patients there were less patients with unfavorable prognosis (ECOG 2 or RPA V), and it resulted in a longer median survival than in the original trial (17 vs. 14.6 months). With this analysis of our patients treated according to the Stupp-protocol for glioblastoma multiforme we validated the results of the original EORTC/NCIC study in a Hungarian patient population. Moreover, this comparison proves that the comprehensive Hungarian neuro-oncology service is not at all inferior when compared to any of the developed countries in Europe.

Journal Title: Magyar onkologia

PUBMED ID: 24352766

DOI: doi.org/10.1007/s11060-013-1316-y

Titolo: Efficacy of erlotinib in patients with relapsed glioblastoma multiforme who expressed EGFRvIII and PTEN determined by immunohistochemistry.

Autori: Gallego O., Cuatrecasas M., Benavides M., Segura PP., Berrocal A., Erill N., Colomer A., Quintana MJ., Balaña C., Gil M., Gallardo A., Murata P., Barnadas A.

Data di Pubblicazione: 2013-12-20

Abstract: Epidermal growth factor receptor gene (EGFR) alteration is a common feature in most of glioblastoma multiforme (GBM). Robust response of anti-EGFR treatments has been mostly associated with the EGFR deletion mutant variant III (EGFRvIII) and expression of PTEN. We have performed a prospective trial in order to confirm the efficacy of erlotinib treatment in patients with relapsed GBM who expressed EGFRvIII and PTEN. All patients included in the trial were required to be PTEN (+++), EGFR (+++) and EGFRvIII (+++) positives by immunohistochemistry. This new phase II trial enrolled 40 patients and was designed to be stopped in case of fewer than two responses in the first 13 patients. Patient eligibility included histopathology criteria, radiological progression, more than 18 years old, Karnofsky performance status, KPS > 50, and adequate bone marrow and organ function. There was no limit to the number of prior treatments for relapses. No enzyme-inducing antiepileptic drugs were allowed. The primary endpoints were response and progression-free survival at 6 months (PFS6). Thirteen patients (6 men, 7 women) with recurrent GBM received erlotinib 150 mg/day. Median age was 53 years, median KPS was 80, and median prior treatments for relapses were 2. There was one partial response and three stable diseases (one at 18 months). PFS at 6 months was 20%. Dose reduction for toxicity was not needed in any patient. Dermatitis was the main treatment-related toxicity, grade 1 in 8 patients and grade 2 in 5

patients. No grade 3 toxicity was observed. Median survival was 7 months (95 % IC 1.41-4.7). As conclusion, monotherapy with erlotinib in GBM relapses patients with high protein expression for PTEN (+++), EGFR (+++), and EGFRvIII (+++) showed low toxicity but minimal efficacy and the trial stopped.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 24347182

DOI: doi.org/10.1177/1352458513516891

Titolo: How to treat tumefactive demyelinating disease?

Autori: Siffrin V., Müller-Forell W., von Pein H., Zipp F.

Data di Pubblicazione: 2013-12-19

Abstract: Glioma-like inflammatory demyelinating lesions can be found in patients with pre-diagnosed multiple sclerosis, but they have also been described as an isolated disease entity. The initial diagnostic work-up usually includes a biopsy for histopathological analysis. However, even after unambiguous histopathologic classification, tumefactive lesions pose a therapeutic challenge. Until now, there have been no guidelines on how to treat patients with these rare and extreme lesion phenotypes. Here we report a patient with a relapsing unifocal tumefactive demyelinating lesion. The patient initially showed a good response to steroid treatment, with full clinical recovery. However, after relapse of the same lesion, recovery was incomplete. Although immunosuppression was initiated, the patient presented with subsequent further deterioration. Only maximal escalation of immunosuppression was able to stop the inflammatory activity. Due to the length of time of the step-wise escalation treatment however, the lengthy lesion activity led to irreversible tissue destruction and residual non-remitting disability. Early aggressive treatment with an induction therapy regimen might be more appropriate for these rare and often strongly disabling lesion subtypes.

Journal Title: Multiple sclerosis (Houndmills, Basingstoke, England)

PUBMED ID: 24339289

DOI: doi.org/10.3349/ymj.2014.55.1.70

Titolo: Feasibility and outcomes of hypofractionated simultaneous integrated boost-intensity modulated radiotherapy for malignant gliomas: a preliminary report.

Autori: Cha J., Suh CO., Park K., Chang JH., Lee KS., Kim SH., Chang JS., Kim JH., Suh YG., Kim JW., Cho J.

Data di Pubblicazione: 2013-12-17

Abstract: An escalated dose of hypofractionated SIB-IMRT using three-layered PTVs can be safely performed in patients with malignant glioma, and might contribute to better tumor control and survival.

Journal Title: Yonsei medical journal

PUBMED ID: 24335695

DOI: doi.org/10.1093/neuonc/not163

Titolo: Benefit from prolonged dose-intensive chemotherapy for infants with malignant brain tumors is restricted to patients with ependymoma: a report of the Pediatric Oncology Group randomized controlled trial 9233/34.

Autori: Strother DR., Lafay-Cousin L., Boyett JM., Burger P., Aronin P., Constance L., Duffner P., Kocak M., Kun LE., Horowitz ME., Gajjar A.

Data di Pubblicazione: 2013-12-17

Abstract: Prolonged dose-intensive chemotherapy given to infants with malignant brain tumors resulted in increased EFS only for patients with ependymoma.

Journal Title: Neuro-oncology



PUBMED ID: 24321226  
DOI: doi.org/10.1016/j.ejrad.2013.06.033  
Titolo: Molecular and metabolic pattern classification for detection of brain glioma progression.  
Autori: Imani F., Boada FE., Lieberman FS., Davis DK., Mountz JM.  
Data di Pubblicazione: 2013-12-11  
Abstract: National Cancer Institute, Cancer Center Support Grant Supplement Award, Imaging Response Assessment Teams.  
Journal Title: European journal of radiology

PUBMED ID: 24311637  
DOI: doi.org/10.1093/neuonc/not161  
Titolo: A single-arm phase II Austrian/German multicenter trial on continuous daily sunitinib in primary glioblastoma at first recurrence (SURGE 01-07).  
Autori: Hutterer M., Nowosielski M., Haybaeck J., Embacher S., Stockhammer F., Gotwald T., Holzner B., Capper D., Preusser M., Marosi C., Oberndorfer S., Moik M., Buchroithner J., Seiz M., Tuettenberg J., Herrlinger U., Wick A., Vajkoczy P., Stockhammer G.  
Data di Pubblicazione: 2013-12-7  
Abstract: Continuous daily sunitinib showed minimal antiglioblastoma activity and substantial toxicity when given at higher doses. High endothelial c-KIT expression may define a subgroup of patients who will benefit from sunitinib treatment by achieving prolonged PFS. ClinicalTrials.gov Identifier: NCT00535379.  
Journal Title: Neuro-oncology

PUBMED ID: 24309609  
DOI: doi.org/10.1097/MPH.0000000000000047  
Titolo: Pediatric phase II trials of poly-ICLC in the management of newly diagnosed and recurrent brain tumors.  
Autori: Hartman LL., Crawford JR., Makale MT., Milburn M., Joshi S., Salazar AM., Hasenauer B., VandenBerg SR., MacDonald TJ., Durden DL.  
Data di Pubblicazione: 2013-12-7  
Abstract: Brain tumors are the most common solid tumor diagnosed in childhood that account for significant morbidity and mortality. New therapies are urgently needed; hence, we conducted the first ever prospective open-label phase II trials of the biological response modifier, poly-ICLC, in children with brain tumors. Poly-ICLC is a synthetic double-stranded RNA that has direct antiviral, antineoplastic, and immune adjuvant effects. A total of 47 children representing a variety of brain tumor histopathologic subtypes were treated with poly-ICLC. On the basis of the results of the initial phase II trial, an expanded prospective phase II trial in low-grade glioma (LGG) has been initiated. MRI was used to acquire volume-based measures of tumor response. No dose-limiting toxicities have been observed. In the initial study 3 of 12 subjects with progressive high-grade gliomas (HGGs) responded, and 2 of 4 children with progressive LGG experienced stable disease for 18 to 24 months. In the follow-up LGG phase II study, 2 of 5 LGG patients were stable over 18 months, with 1 stable for 6 months. Overall 5 of 10 LGG patients have responded. On the basis of low toxicity and the promising LGG response, poly-ICLC may be effective for childhood LGG, and the results justify biomarker studies for personalization of poly-ICLC as a single agent or adjuvant.  
Journal Title: Journal of pediatric hematology/oncology

PUBMED ID: 24305706  
DOI: doi.org/10.1093/neuonc/not169  
Titolo: Clinical and prognostic features of adult patients with gangliogliomas.

Autori: Yust-Katz S., Anderson MD., Liu D., Wu J., Yuan Y., Olar A., Fuller GN., Brown PD., de-Groot JF.

Data di Pubblicazione: 2013-12-6

Abstract: While GG has excellent prognosis, malignant histologic grade, older age, and diagnosis with biopsy could indicate worse prognosis. The late nature and high rate of progression emphasize the importance of long-term follow-up. The role of chemotherapy and radiation therapy for incompletely resected low-grade GG remains unclear.

Journal Title: Neuro-oncology

PUBMED ID: 24293233

DOI: doi.org/10.1007/s11060-013-1317-x

Titolo: Bevacizumab and fotemustine for recurrent glioblastoma: a phase II study of AINO (Italian Association of Neuro-Oncology).

Autori: Soffietti R., Trevisan E., Bertero L., Cassoni P., Morra I., Fabrini MG., Pasqualetti F., Lolli I., Castiglione A., Ciccone G., Rudà R.

Data di Pubblicazione: 2013-12-3

Abstract: The optimal combination of bevacizumab with cytotoxic or cytostatic drugs in recurrent glioblastoma is unknown. We performed a phase 2 trial of combined bevacizumab and fotemustine for patients with glioblastoma at first relapse after radiotherapy and temozolomide. The primary endpoint was 6-month progression-free survival (PFS), while secondary endpoints were overall survival (OS), response rate based on RANO criteria and toxicity. Fifty-four patients with recurrent GBM were enrolled. The authors observed a 6-month PFS rate of 42.6% (95% CI 29.3-55.2) and a median PFS of 5.2 months (95% CI 3.8-6.6). The median OS was 9.1 months (95% CI 7.3-10.3). Twenty-eight patients (52%) had a radiographic response, and a significant neurological improvement with steroid reduction was observed in 25/42 symptomatic patients (60%). MGMT promoter methylation was significantly associated with improved PFS in univariate analysis. Most unifocal tumors at baseline had a focal enhancing progression (76%), while the diffuse non-enhancing progression accounted for 9.5%. Response or survival were not associated with any pattern of progression. Survival after failure of treatment was short. Twelve out of 54 patients (22%) discontinued fotemustine for grade 3/4 myelotoxicity, while 4/54 (7.4%) discontinued bevacizumab. This study failed to demonstrate a superiority of the combination of bevacizumab and fotemustine over either bevacizumab or fotemustine alone as historical controls. Future studies should explore alternative regimens of combination of the two drugs.

Journal Title: Journal of neuro-oncology

PUBMED ID: 24286144

DOI: doi.org/10.3171/2013.10.JNS131512

Titolo: Delayed leptomeningeal and subependymal seeding after multiple surgeries for supratentorial diffuse low-grade gliomas in adults.

Autori: Alvarez de Eulate-Beramendi S., Rigau V., Taillandier L., Duffau H.

Data di Pubblicazione: 2013-11-30

Abstract: Cerebrospinal fluid dissemination of DLGG is a rare but possible event. It can occur throughout the progression of WHO Grade II oligodendrogliomas, oligoastrocytomas, and astrocytomas, regardless of 1p19q status. This complication seems to appear in patients who have undergone multiple incomplete resections. Salvage therapy can be considered in patients with good neurological status. However, LMSS is associated with a decreased overall survival. Therefore, this rare entity deserves further multicenter studies to better understand its pathophysiology and to adapt therapeutic strategies.

Journal Title: Journal of neurosurgery

PUBMED ID: 24218181

DOI: doi.org/10.1007/s11060-013-1284-2

Titolo: Favorable survival and metabolic outcome for children with diencephalic syndrome using a radiation-sparing approach.

Autori: Kilday JP., Bartels U., Huang A., Barron M., Shago M., Mistry M., Zhukova N., Laperriere N., Dirks P., Hawkins C., Bouffet E., Tabori U.

Data di Pubblicazione: 2013-11-13

Abstract: Diencephalic syndrome (DS) is a clinical disorder of metabolism associated with poor outcome in children with low-grade gliomas (LGGs). Since survival has been primarily reported with aggressive therapy, we report outcome data for these patients using a current, contrasting chemotherapy-driven approach. We performed a population-based review of DS patients treated with chemotherapy from 1997-2012. Metabolic rate was assessed in selected cases using open-circuit calorimetry to generate resting energy expenditure (REE) data. Tumor tissue was analyzed for BRAF alterations. Survival was compared with an age-related, radiotherapy naïve cohort of non-DS children with location-matched LGGs. Nine children (1.7% of 520 LGG diagnoses) fulfilled DS criteria. The median diagnostic age was 1.49 years (0.55-2.69 years), although neurofibromatosis Type-I patients were older ( $p = 0.005$ ). All tumors analyzed exhibited either NF1 mutation or BRAF fusion. Seven tumors were histologically confirmed as low grade astrocytomas, one demonstrated neurocytic features, and one NF1 case was diagnosed using imaging and clinical criteria. All patients received chemotherapy, with seven cases also receiving initial nutritional supplementation. All nine gained weight after only 6 months of treatment. Two DS patients had serial REE measurements, revealing a hypermetabolic state (over 200% of predicted REE) at diagnosis which reduced to normal range with therapy. First-line chemotherapy treatment resulted in one minor response, stable disease in four cases, with progression in the remaining four patients. Although DS patients demonstrated inferior initial progression-free survival when compared to non-DS counterparts (5 years: 22 versus 60%,  $p = 0.015$ ), all DS children remain alive at a median follow up of 5.3 years (1.2-14.9 years) with none requiring radiotherapy. Long-term sequelae included pituitary and visual dysfunction, learning difficulties and paradoxical, inappropriate weight gain. DS can be managed with non-aggressive chemotherapeutic, radiation-sparing strategies supplemented by temporary nutritional support. Multiple lines of therapy may be required to overcome disease progression but excellent survival and metabolic outcomes can be achieved. Continued surveillance is mandatory to prevent significant weight gain and support affected children with clinical sequelae.

Journal Title: Journal of neuro-oncology

PUBMED ID: 24202340

DOI: doi.org/10.3390/cancers5031177

Titolo: Outcomes in newly diagnosed elderly glioblastoma patients after concomitant temozolomide administration and hypofractionated radiotherapy.

Autori: Nguyen LT., Touch S., Nehme-Schuster H., Antoni D., Eav S., Clavier JB., Bauer N., Vigneron C., Schott R., Kehrli P., Noël G.

Data di Pubblicazione: 2013-11-9

Abstract: This study aimed to analyze the treatment and outcomes of older glioblastoma patients. Forty-four patients older than 70 years of age were referred to the Paul Strauss Center for chemotherapy and radiotherapy. The median age was 75.5 years old (range: 70-84), and the patients included 18 females and 26 males. The median Karnofsky index (KI) was 70%. The Charlson indices varied from 4 to 6. All of the patients underwent surgery. O6-methylguanine-DNA methyltransferase (MGMT) methylation status was determined in 25 patients. All of the patients received radiation therapy. Thirty-eight patients adhered to a hypofractionated radiation therapy schedule and six patients to a normofractionated schedule. Neoadjuvant, concomitant and adjuvant chemotherapy regimens were administered to 12, 35 and 20 patients, respectively. At the time of this analysis, 41 patients had died. The median time to relapse

was 6.7 months. Twenty-nine patients relapsed, and 10 patients received chemotherapy upon relapse. The median overall survival (OS) was 7.2 months and the one- and two-year OS rates were 32% and 12%, respectively. In a multivariate analysis, only the Karnofsky index was a prognostic factor. Hypofractionated radiotherapy and chemotherapy with temozolomide are feasible and acceptably tolerated in older patients. However, relevant prognostic factors are needed to optimize treatment proposals.

Journal Title: Cancers

PUBMED ID: 24190997

DOI: doi.org/10.1073/pnas.1318022110

Titolo: Improved tumor oxygenation and survival in glioblastoma patients who show increased blood perfusion after cediranib and chemoradiation.

Autori: Batchelor TT., Gerstner ER., Emblem KE., Duda DG., Kalpathy-Cramer J., Snuderl M., Ancukiewicz M., Polaskova P., Pinho MC., Jennings D., Plotkin SR., Chi AS., Eichler AF., Dietrich J., Hochberg FH., Lu-Emerson C., Iafrate AJ., Ivy SP., Rosen BR., Loeffler JS., Wen PY., Sorensen AG., Jain RK.

Data di Pubblicazione: 2013-11-6

Abstract: Antiangiogenic therapy has shown clear activity and improved survival benefit for certain tumor types. However, an incomplete understanding of the mechanisms of action of antiangiogenic agents has hindered optimization and broader application of this new therapeutic modality. In particular, the impact of antiangiogenic therapy on tumor blood flow and oxygenation status (i.e., the role of vessel pruning versus normalization) remains controversial. This controversy has become critical as multiple phase III trials of anti-VEGF agents combined with cytotoxics failed to show overall survival benefit in newly diagnosed glioblastoma (nGBM) patients and several other cancers. Here, we shed light on mechanisms of nGBM response to cediranib, a pan-VEGF receptor tyrosine kinase inhibitor, using MRI techniques and blood biomarkers in prospective phase II clinical trials of cediranib with chemoradiation vs. chemoradiation alone in nGBM patients. We demonstrate that improved perfusion occurs only in a subset of patients in cediranib-containing regimens, and is associated with improved overall survival in these nGBM patients. Moreover, an increase in perfusion is associated with improved tumor oxygenation status as well as with pharmacodynamic biomarkers, such as changes in plasma placenta growth factor and sVEGFR2. Finally, treatment resistance was associated with elevated plasma IL-8 and sVEGFR1 posttherapy. In conclusion, tumor perfusion changes after antiangiogenic therapy may distinguish responders vs. nonresponders early in the course of this expensive and potentially toxic form of therapy, and these results may provide new insight into the selection of glioblastoma patients most likely to benefit from anti-VEGF treatments.

Journal Title: Proceedings of the National Academy of Sciences of the United States of America

PUBMED ID: 24105052

DOI: Mancante

Titolo: [Chemotherapy for malignant gliomas: an update].

Autori: Wakabayashi T., Natsume A., Fujii M.

Data di Pubblicazione: 2013-10-10

Abstract: Gliomas account for approximately 30% of all brain tumors and are thus the most common primary tumors of the central nervous system (CNS). Despite treatment with aggressive surgical resection, chemotherapy, and radiotherapy, high-grade (WHO grades III and IV) malignant gliomas, especially glioblastoma (GBM), the most common glioma in adults, kill patients within a median time span of a year after diagnosis. In Japan, alkylating agents such as 1-(4-amino-2-methyl-5-pyridiminy) methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU) and methyl-6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-alpha-D-glucopyranoside (MCNU) have been used to treat malignant gliomas for a long time;

however, this treatment provides few clinical benefits. Temozolomide (TMZ), an oral alkylating agent, has been demonstrated to possess antitumor activity against malignant gliomas with minimal additional toxicity; furthermore, a previous study found that treatment with TMZ significantly prolonged median survival time. In 2006, TMZ was certified as the treatment agent for malignant gliomas by the National Ministry of Health and Welfare of Japan. It is now used as first-line therapy. However, its clinical outcomes depend on the O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) status, and MGMT modification is one of the key factors to deriving greater clinical benefits in the future. Combination therapy with TMZ and other antitumor drugs, especially anti-vascular endothelial growth factor (VEGF) antibody (Avascine), has been aggressively investigated for treating gliomas. Some of these drugs have been studied in experimental animal models and advanced to clinical trials. These studies suggest that combination therapy with TMZ and other antitumor drugs might further improve the clinical outcome of malignant gliomas as compared to TMZ plus radiotherapy. Based on these data, the next step will be to carry out phase II to III clinical studies to improve treatment of malignant brain tumors further.

Journal Title: Gan to kagaku ryoho. Cancer & chemotherapy

PUBMED ID: 24077351

DOI: doi.org/10.1158/1078-0432.CCR-13-1425

Titolo: Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a pediatric brain tumor consortium study.

Autori: Gajjar A., Stewart CF., Ellison DW., Kaste S., Kun LE., Packer RJ., Goldman S., Chintagumpala M., Wallace D., Takebe N., Boyett JM., Gilbertson RJ., Curran T.

Data di Pubblicazione: 2013-10-1

Abstract: Vismodegib was well tolerated in children with recurrent or refractory medulloblastoma; only two dose-limiting toxicities were observed with flat dosing. The recommended phase II study dose is 150 or 300 mg, depending on the patient's BSA. Clin Cancer Res; 19(22); 6305-12. ©2013 AACR.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 24076268

DOI: doi.org/10.1016/j.pharmthera.2013.09.003

Titolo: Bevacizumab and micrometastases: revisiting the preclinical and clinical rollercoaster.

Autori: Mountzios G., Pentheroudakis G., Carmeliet P.

Data di Pubblicazione: 2013-10-1

Abstract: The use of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), in combination with standard therapeutic approaches, has offered clinical benefit for patients with advanced colorectal, breast, ovarian, renal, non small-cell lung cancer and glioblastoma. However, the strategy of administering bevacizumab until disease progression has been challenged by certain preclinical evidence, suggesting that prolonged exposure to anti-VEGF treatment may elicit an adaptive-evasive response, resulting in a more aggressive tumor phenotype. Moreover, the use of bevacizumab in adjuvant chemotherapeutic regimens has led to less promising results than expected. Despite our poor understanding of how bevacizumab acts in micrometastatic disease, numerous clinical trials (involving >20,000 cancer patients) are ongoing or are planned to test the therapeutic benefit in the adjuvant setting. The discrepancy of bevacizumab's efficiency in the two settings calls into question the validity of current strategies that use similar treatment regimens for early and advanced diseases. Herein, we review the mechanisms of bevacizumab activity in the macro- as compared to the micrometastatic environment and discuss possible alternative strategies in the adjuvant setting.

ng that might spur attention for future clinical trials. Rather than providing an encyclopedic survey of the literature, we highlight exemplary principles.

Journal Title: Pharmacology & therapeutics

PUBMED ID: 24066926

DOI: doi.org/10.1186/1748-717X-8-222

Titolo: Hypofractionated stereotactic radiation therapy for recurrent glioblastoma: single institutional experience.

Autori: Ciammella P., Podgornii A., Galeandro M., D'Abbiero N., Pisanello A., Botti A., Cagni E., Iori M., Iotti C.

Data di Pubblicazione: 2013-9-27

Abstract: Our results suggest that hypofractionated stereotactic radiation therapy is effective and safe in recurrent GBM. However, until prospective randomized trials will confirm these results, the decision for salvage treatment should remain individual and based on a multidisciplinary evaluation of each patient.

Journal Title: Radiation oncology (London, England)

PUBMED ID: 24050762

DOI: doi.org/10.3109/08880018.2013.829895

Titolo: Treatment of children with diffuse intrinsic pontine gliomas with chemoradiotherapy followed by a combination of temozolomide, irinotecan, and bevacizumab.

Autori: Zaky W., Wellner M., Brown RJ., Blüml S., Finlay JL., Dhall G.

Data di Pubblicazione: 2013-9-21

Abstract: This augmented regimen was associated with increased but tolerable toxicity and a modest increase in EFS and OS when compared with published literature in patients with DIPG (median EFS and OS of 6.1 and 9.6 months, respectively). More effective therapies are desperately needed.

Journal Title: Pediatric hematology and oncology

PUBMED ID: 24046261

DOI: doi.org/10.1093/neuonc/not126

Titolo: Stereotactic iodine-125 brachytherapy for the treatment of WHO grade II and III gliomas located in the central sulcus region.

Autori: Ruge MI., Kickingeder P., Grau S., Dorn F., Galldiks N., Treuer H., Sturm V.

Data di Pubblicazione: 2013-9-19

Abstract: Compared with microsurgical resection, SBT harbors a low risk of procedural complications, is minimally invasive, and seems to be an effective local treatment option for patients with inoperable, eloquent WHO grade II and III gliomas in the CSR. However, the value of SBT for treating gliomas still needs to be determined in prospective, randomized studies.

Journal Title: Neuro-oncology

PUBMED ID: 24011536

DOI: doi.org/10.1016/j.ejca.2013.08.006

Titolo: Diffuse intrinsic pontine glioma treated with prolonged temozolomide and radiotherapy--results of a United Kingdom phase II trial (CNS 2007 04).

Autori: Bailey S., Howman A., Wheatley K., Wherton D., Boota N., Pizer B., Fisher D., Kearns P., Picton S., Saran F., Gibson M., Glaser A., Connolly DJ., Hargrave D.

Data di Pubblicazione: 2013-9-10

Abstract: Diffuse intrinsic pontine glioma (DIPG) has a dismal prognosis with no chemotherapy regimen so far resulting in any significant improvement over

er standard radiotherapy. In this trial, a prolonged regimen (21/28d) of temozolomide was studied with the aim of overcoming O(6)-methylguanine methyltransferase (MGMT) mediated resistance. Forty-three patients with a defined clinico-radiological diagnosis of DIPG received radiotherapy and concomitant temozolomide (75 mg/m<sup>2</sup>) after which up to 12 courses of 21d of adjuvant temozolomide (75-100mg/m<sup>2</sup>) were given 4 weekly. The trial used a 2-stage design and passed interim analysis. At diagnosis median age was 8 years (2-20 years), 81% had cranial nerve abnormalities, 76% ataxia and 57% long tract signs. Median Karnofsky/Lansky score was 80 (10-100). Patients received a median of three courses of adjuvant temozolomide, five received all 12 courses and seven did not start adjuvant treatment. Three patients were withdrawn from study treatment due to haematological toxicity and 10 had a dose reduction. No other significant toxicity related to temozolomide was noted. Overall survival (OS) (95% confidence interval (CI)) was 56% (40%, 69%) at 9 months, 35% (21%, 49%) at 1 year and 17% (7%, 30%) at 2 years. Median survival was 9.5 months (range 7.5-11.4 months). There were five 2-year survivors with a median age of 13.6 years at diagnosis. This trial demonstrated no survival benefit of the addition of dose dense temozolomide, to standard radiotherapy in children with classical DIPG. However, a subgroup of adolescent DIPG patients did have a prolonged survival, which needs further exploration.  
Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 24008924

DOI: doi.org/10.1159/000354692

Titolo: FLAIR-only progression in bevacizumab-treated relapsing glioblastoma does not predict short survival.

Autori: Schaub C., Greschus S., Seifert M., Waha A., Blasius E., Rasch K., Landwehr C., Mack F., Schäfer N., Stuplich M., Kebir S., Vilz B., Scheffler B., Boström J., Simon M., Urbach H., Glas M., Herrlinger U.

Data di Pubblicazione: 2013-9-7

Abstract: FLAIR-only progression is not an independent prognostic factor negatively influencing OS in recurrent glioblastoma treated with bevacizumab and should not lead to discontinuation of bevacizumab therapy.

Journal Title: Oncology

PUBMED ID: 24002900

DOI: doi.org/10.1093/jjco/hyt124

Titolo: Phase I study of bevacizumab plus irinotecan in pediatric patients with recurrent/refractory solid tumors.

Autori: Okada K., Yamasaki K., Tanaka C., Fujisaki H., Osugi Y., Hara J.

Data di Pubblicazione: 2013-9-5

Abstract: Combination chemotherapy of bevacizumab plus irinotecan was well tolerated in children. We plan Phase II pediatric studies at doses of bevacizumab 10 mg/kg and irinotecan 100 mg/m<sup>2</sup> every 2 weeks (270 mg/m<sup>2</sup> for patients taking enzyme-inducing antiepileptic drugs).

Journal Title: Japanese journal of clinical oncology

PUBMED ID: 23957780

DOI: doi.org/10.3109/02688697.2013.829554

Titolo: Stupp-treated glioblastoma accompanied by EBV-positive primary CNS lymphoma.

Autori: Zakaria Z., Fenton E., Khalil A., Sattar MT., Molnar P.

Data di Pubblicazione: 2013-8-21

Abstract: We describe a patient who within 2 months of undergoing radio-chemotherapy for glioblastoma developed an Epstein-Barr virus-positive primary diffuse large B-cell CNS lymphoma. To our knowledge, this is the first such case.

ase reported in the literature showing that new tumefactions following aggressive treatment for glioblastomata might represent secondary malignancies.  
Journal Title: British journal of neurosurgery

PUBMED ID: 23952800

DOI: doi.org/10.3171/2013.7.JNS13415

Titolo: Phase II clinical study on intraoperative photodynamic therapy with talaporfin sodium and semiconductor laser in patients with malignant brain tumors.

Autori: Muragaki Y., Akimoto J., Maruyama T., Iseki H., Ikuta S., Nitta M., Maebayashi K., Saito T., Okada Y., Kaneko S., Matsumura A., Kuroiwa T., Karasawa K., Nakazato Y., Kayama T.

Data di Pubblicazione: 2013-8-20

Abstract: Intraoperative PDT using talaporfin sodium and a semiconductor laser may be considered as a potentially effective and sufficiently safe option for adjuvant management of primary malignant parenchymal brain tumors. The inclusion of intraoperative PDT in a combined treatment strategy may have a positive impact on OS and local tumor control, particularly in patients with newly diagnosed GBMs. Clinical trial registration no.: JMA-IIA00026 (<https://dbcentre3.jmacct.med.or.jp/jmacctr/App/JMACTRS06/JMACTRS06.aspx?seqno=862>).

Journal Title: Journal of neurosurgery

PUBMED ID: 23927666

DOI: doi.org/10.1586/17512433.2013.811806

Titolo: An EGFRvIII-targeted bispecific T-cell engager overcomes limitations of the standard of care for glioblastoma.

Autori: Gedeon PC., Choi BD., Hodges TR., Mitchell DA., Bigner DD., Sampson JH.

Data di Pubblicazione: 2013-8-10

Abstract: While advanced surgical techniques, radiation therapy and chemotherapeutic regimens provide a tangible benefit for patients with glioblastoma (GBM), the average survival from the time of diagnosis remains less than 15 months. Current therapy for GBM is limited by the nonspecific nature of treatment, prohibiting therapy that is aggressive and prolonged enough to eliminate all malignant cells. As an alternative, bispecific antibodies can redirect the immune system to eliminate malignant cells with exquisite potency and specificity. We have recently developed an EGF receptor variant III (EGFRvIII)-targeted bispecific antibody that redirects T cells to eliminate EGFRvIII-expressing GBM. The absolute tumor specificity of EGFRvIII and the lack of immunologic crossreactivity with healthy cells allow this therapeutic to overcome limitations associated with the nonspecific nature of the current standard of care for GBM. Evidence indicates that the molecule can exert therapeutically significant effects in the CNS following systemic administration. Additional advantages in terms of ease-of-production and off-the-shelf availability further the clinical utility of this class of therapeutics.

Journal Title: Expert review of clinical pharmacology

PUBMED ID: 23909061

DOI: Mancante

Titolo: Tailored therapy in diffuse gliomas: using molecular classifiers to optimize clinical management.

Autori: Taylor JW., Chi AS., Cahill DP.

Data di Pubblicazione: 2013-8-6

Abstract: Diffuse gliomas are the most common primary malignant brain tumors in adults and continue to be almost universally fatal. Nevertheless, a striking variability in outcome has long been observed, with a subset of patients having prolonged survival. Recent molecular discoveries have provided new in



sights into gliomagenesis and have enhanced clinical subclassification of gliomas. Mutations in the isocitrate dehydrogenase (IDH) genes occur frequently in low-grade astrocytomas and oligodendrogliomas (World Health Organization [WHO] grade II), and in higher-grade gliomas (WHO grades III and IV) that arise after malignant progression of low-grade tumors. IDH mutation has an established role as a favorable prognostic marker; however, the utility of IDH mutation in guiding treatment is still under investigation. A subset of IDH-mutant tumors, predominantly oligodendrogliomas, also harbor codeletion of chromosomes 1p and 19q, a feature that predicts responsiveness to chemotherapy. Here, we review the current data regarding the prognostic and predictive value of IDH mutation and 1p/19q codeletion in gliomas. We also discuss possible management algorithms using these biomarkers to tailor surgical and adjuvant therapy for specific diffuse gliomas. Ultimately, understanding the natural history of glioma subtypes and the predictive value of genetic markers may maximize survival and minimize treatment morbidity.  
Journal Title: Oncology (Williston Park, N.Y.)

PUBMED ID: 23898108

DOI: Mancante

Titolo: Continuous tamoxifen and dose-dense temozolomide in recurrent glioblastoma.

Autori: DI Cristofori A., Carrabba G., Lanfranchi G., Menghetti C., Rampini P., Caroli M.

Data di Pubblicazione: 2013-7-31

Abstract: The combinatorial administration of tamoxifen and TMZ appeared to be well-tolerated, and potentially effective in increasing the efficacy of dose-dense TMZ schedule as a second-line therapeutic strategy.

Journal Title: Anticancer research

PUBMED ID: 23883555

DOI: doi.org/10.2176/nmc.53.447

Titolo: Updated therapeutic strategy for adult low-grade glioma stratified by resection and tumor subtype.

Autori: Nitta M., Muragaki Y., Maruyama T., Iseki H., Ikuta S., Konishi Y., Saito T., Tamura M., Chernov M., Watanabe A., Okamoto S., Maebayashi K., Mitsuhashi N., Okada Y.

Data di Pubblicazione: 2013-7-26

Abstract: The importance of surgical resection for patients with supratentorial low-grade glioma (LGG) remains controversial. This retrospective study of patients (n = 153) treated between 2000 to 2010 at a single institution assessed whether increasing the extent of resection (EOR) was associated with improved progression-free survival (PFS) and overall survival (OS). Histological subtypes of World Health Organization grade II tumors were as follows: diffuse astrocytoma in 49 patients (32.0%), oligoastrocytoma in 45 patients (29.4%), and oligodendroglioma in 59 patients (38.6%). Median pre- and postoperative tumor volumes and median EOR were 29.0 cm<sup>3</sup> (range 0.7-162 cm<sup>3</sup>) and 1.7 cm<sup>3</sup> (range 0-135.7 cm<sup>3</sup>) and 95%, respectively. Five- and 10-year OS for all LGG patients were 95.1% and 85.4%, respectively. Eight-year OS for diffuse astrocytoma, oligoastrocytoma, and oligodendroglioma were 70.7%, 91.2%, and 98.3%, respectively. Five-year PFS for diffuse astrocytoma, oligoastrocytoma, and oligodendroglioma were 42.6%, 71.3%, and 62.7%, respectively. Patients were divided into two groups by EOR  $\geq 90\%$  and  $<90\%$ , and OS and PFS were analyzed. Both OS and PFS were significantly longer in patients with  $\geq 90\%$  EOR. Increased EOR resulted in better PFS for diffuse astrocytoma but not for oligodendroglioma. Multivariate analysis identified age and EOR as parameters significantly associated with OS. The only parameter associated with PFS was EOR. Based on these findings, we established updated therapeutic strategies for LGG. If surgery resulted in EOR  $<90\%$ , patients with astrocytoma w

ill require second-look surgery, whereas patients with oligodendroglioma or oligoastrocytoma, which are sensitive to chemotherapy, will be treated with chemotherapy.

Journal Title: Neurologia medico-chirurgica

PUBMED ID: 23883553

DOI: doi.org/10.2176/nmc.53.429

Titolo: Current knowledge and treatment strategies for grade II gliomas.

Autori: Narita Y.

Data di Pubblicazione: 2013-7-26

Abstract: World Health Organization grade II gliomas (GIIGs) include diffuse astrocytoma, oligodendroglioma, and oligoastrocytoma. GIIG is a malignant brain tumor for which the treatment outcome can still be improved. Review of previous clinical trials found the following: (1) GIIG increased in size by 3-5 mm per year when observed or treated with surgery alone; (2) after pathological diagnosis, the survival rate was increased by early aggressive tumor removal at an earlier stage compared to observation alone; (3) although the prognosis after total tumor removal was significantly better than that after partial tumor removal, half of the patients relapsed within 5 years; (4) comparing postoperative early radiotherapy (RT) and non-early RT after relapse, early RT prolonged progression-free survival (PFS) but did not affect overall survival (OS); (5) local RT of 45 to 64.8 Gy did not impact PFS or OS; (6) in patients with residual tumors, RT combined with chemotherapy (procarbazine plus lomustine plus vincristine) prolonged PFS compared with RT alone but did not affect OS; and (7) poor prognostic factors included astrocytoma, non-total tumor removal, age  $\geq 40$  years, largest tumor diameter  $\geq 4$ -6 cm, tumor crossing the midline, and neurological deficit. To improve treatment outcomes, surgery with functional brain mapping or intraoperative magnetic resonance imaging or chemoradiotherapy with temozolomide is important. In this review, current knowledge regarding GIIG is described and treatment strategies are explored.

Journal Title: Neurologia medico-chirurgica

PUBMED ID: 23870041

DOI: doi.org/10.3171/2013.6.PEDS12586

Titolo: Neurosurgical treatment of oligodendroglial tumors in children and adolescents: a single-institution series of 35 consecutive patients.

Autori: Lundar T., Due-Tønnessen BJ., Egge A., Scheie D., Stensvold E., Brandal P.

Data di Pubblicazione: 2013-7-23

Abstract: Pediatric oligodendroglial tumors are mainly localized to the supratentorial compartment and more often occur in the 2nd decade of life rather than the 1st. Two-thirds of the patients remained alive after follow-ups from 4 to 31 years. Twelve children succumbed to their disease, 9 of them within 3 years of resection despite combined treatment with radio- and chemotherapy. Three of them remained alive from 9 to 33 years after primary resection. Among the 23 survivors, a stable, very long-term result was attainable in at least 20. Five-, 10-, 20-, and 30-year overall survival in patients with Grade II tumors was 92%, 92%, 92%, and 88%, respectively.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 23831852

DOI: doi.org/10.1007/s00066-013-0357-7

Titolo: Radiotherapy in pediatric pilocytic astrocytomas. A subgroup analysis within the prospective multicenter study HIT-LGG 1996 by the German Society of Pediatric Oncology and Hematology (GPOH).

Autori: Müller K., Gnekow A., Falkenstein F., Scheiderbauer J., Zwiener I., Pietsch T., Warmuth-Metz M., Voges J., Nikkhah G., Flentje M., Combs SE., Vordermark D., Kocher M., Kortmann RD.

Data di Pubblicazione: 2013-7-9

Abstract: EFRT plays an integral role in the treatment of pediatric pilocytic astrocytoma and is characterized by excellent tumor control. A reduction of the normalized total dose from 54 to 50.4 Gy appears to be feasible without jeopardizing tumor control. SBT is an effective treatment alternative.

Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 23813229

DOI: doi.org/10.1007/s11060-013-1189-0

Titolo: Clinico-radiologic characteristics of long-term survivors of diffuse intrinsic pontine glioma.

Autori: Jackson S., Patay Z., Howarth R., Pai Panandiker AS., Onar-Thomas A., Gajjar A., Broniscer A.

Data di Pubblicazione: 2013-7-2

Abstract: Diffuse intrinsic pontine glioma (DIPG) is the deadliest central nervous system tumor in children. The survival of affected children has remained poor despite treatment with radiation therapy (RT) with or without chemotherapy. We reviewed the medical records of all surviving patients with DIPG treated at our institution between October 1, 1992 and May 31, 2011. Blinded central radiologic review of the magnetic resonance imaging at diagnosis of all surviving patients and 15 controls with DIPG was performed. All surviving patients underwent neurocognitive assessment during follow-up. Five (2.6 %) of 191 patients treated during the study period were surviving at a median of 9.3 years from their diagnosis (range 5.3-13.2 years). Two patients were younger than 3 years, one lacked signs of pontine cranial nerve involvement, and three had longer duration of symptoms at diagnosis. One patient had a radiologically atypical tumor and one had a tumor originating in the medulla. All five patients received RT. Chemotherapy was variable among these patients. Neurocognitive assessments were obtained after a median interval of 7.1 years. Three of four patients who underwent a detailed evaluation showed cognitive function in the borderline or mental retardation range. Two patients experienced disease progression at 8.8 and 13 years after diagnosis. A minority of children with DIPG experienced long-term survival with currently available therapies. These patients remained at high risk for tumor progression even after long follow-ups. Four of our long-term survivors had clinical and radiologic characteristics at diagnosis associated with improved outcome.

Journal Title: Journal of neuro-oncology

PUBMED ID: 23749916

DOI: Mancante

Titolo: Wide-field pulsed reduced dose rate radiotherapy (PRDR) for recurrent ependymoma in pediatric and young adult patients.

Autori: Mohindra P., Robins HI., Tomé WA., Hayes L., Howard SP.

Data di Pubblicazione: 2013-6-11

Abstract: In patients with large-volume recurrent ependymoma, re-irradiation with wide-field PRDR is a feasible option.

Journal Title: Anticancer research

PUBMED ID: 23721146

DOI: doi.org/10.1111/j.1754-9485.2012.02472.x

Titolo: MRI patterns of T1 enhancing radiation necrosis versus tumour recurrence in high-grade gliomas.

Autori: Reddy K., Westerly D., Chen C.

Data di Pubblicazione: 2013-6-1

Abstract: Identifying distinct patterns of contrast enhancement on MRI may help to differentiate between radiation necrosis and tumour recurrence in high-grade gliomas.

Journal Title: Journal of medical imaging and radiation oncology

PUBMED ID: 23670807

DOI: doi.org/10.1055/s-0033-1342938

Titolo: Cerebellar anaplastic astrocytoma in an adult with neurofibromatosis type 1: case report and review of literature.

Autori: Brokinkel B., Schober O., Ewelt C., Heindel W., Hargus G., Stummer W., Holling M., Wölfer J.

Data di Pubblicazione: 2013-5-15

Abstract: A literature search yielded only one previously published case of an AA in a 9-year-old girl with NF1. Tumor control after resection was achieved in both patients; however, the patient in the mentioned report received radiation instead of temozolomide. In spite of different adjuvant therapies, tumor control for at least 16 months was achieved in both published cases. Thus, even though the role of adjuvant treatment options remains to be further elucidated, surgery is the appropriate therapy in these uncommon tumors providing mass reduction and histological diagnosis as well as tumor control.

Journal Title: Journal of neurological surgery. Part A, Central European neurosurgery

PUBMED ID: 23634286

DOI: doi.org/10.1002/cam4.58

Titolo: Phase II trial of upfront bevacizumab and temozolomide for unresectable or multifocal glioblastoma.

Autori: Lou E., Peters KB., Sumrall AL., Desjardins A., Reardon DA., Lipp ES., Herndon JE., Coan A., Bailey L., Turner S., Friedman HS., Vredenburgh JJ.

Data di Pubblicazione: 2013-5-2

Abstract: Patients with unresectable glioblastomas have a poor prognosis, with median survival of 6-10 months. We conducted a phase II trial of upfront 5-day temozolomide (TMZ) and bevacizumab (BV) in patients with newly diagnosed unresectable or multifocal glioblastoma. Patients received up to four cycles of TMZ at 200 mg/m<sup>2</sup> on days 1-5, and BV at 10 mg/kg on days 1 and 15 of a 28-day cycle. Brain magnetic resonance imaging (MRI) was performed monthly. Therapy was continued as long as there was no tumor progression, grade 4 nonhematologic toxicity, or recurrent grade 4 hematologic toxicity after dose reduction. The primary end point was best tumor response as measured on MRI. Forty-one patients were accrued over 12 months; 39 had a full set of MRI scans available for evaluation. Assessment for best radiographic responses was as follows: partial responses in 24.4%, stable disease in 68.3%, and progressive disease in 2.4%. Treatment-related toxicities included seven grade 4 toxicities and one grade 5 toxicity (myocardial infarction). From this study, it was concluded that an upfront regimen of TMZ and BV for unresectable glioblastoma was well tolerated and provided a significant level of disease stabilization. Therapeutic toxicities were consistent with those seen in the adjuvant setting using these agents. The upfront approach to treatment of glioblastoma in the unresectable population warrants further investigation in randomized controlled phase III trials.

Journal Title: Cancer medicine

PUBMED ID: 23630166

DOI: doi.org/10.1158/1078-0432.CCR-12-2119

Titolo: Prolonged inhibition of glioblastoma xenograft initiation and clonogenic growth following in vivo Notch blockade.

Autori: Chu Q., Orr BA., Semenkow S., Bar EE., Eberhart CG.

Data di Pubblicazione: 2013-5-1

Abstract: Weekly oral delivery of MRK003 results in significant in vivo inhibition of Notch pathway activity, tumor growth, stem cell marker expression, and clonogenicity, providing preclinical support for the use of such compounds in patients with malignant brain tumors. Some of these effects can persist for some time after in vivo therapy is complete.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 23595805

DOI: doi.org/10.1007/s00381-013-2104-x

Titolo: Relapse in medulloblastoma: what can be done after abandoning high-dose chemotherapy? A mono-institutional experience.

Autori: Massimino M., Casanova M., Polastri D., Biassoni V., Modena P., Pecori E., Schiavello E., De Pava MV., Indini A., Rampini P., Bauer D., Catania S., Podda M., Gandola L.

Data di Pubblicazione: 2013-4-19

Abstract: Without succeeding in patients cure, we ensured them further treatment with short hospital stay thus affording low personal and social costs. The chances of cure may emerge from tailored therapies according to genetic stratification.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 23578667

DOI: doi.org/10.3174/ajnr.A3506

Titolo: Longitudinal restriction spectrum imaging is resistant to pseudoresponse in patients with high-grade gliomas treated with bevacizumab.

Autori: Kothari P., White NS., Farid N., Chung R., Kuperman JM., Girard HM., Shankaranarayanan A., Kesari S., McDonald CR., Dale AM.

Data di Pubblicazione: 2013-4-13

Abstract: Restriction spectrum imaging is less influenced by reductions in F LAIR hyperintensity compared with ADC, which may confer an advantage of restriction spectrum imaging over ADC for interpreting tumor response on imaging following antiangiogenic therapy.

Journal Title: AJNR. American journal of neuroradiology

PUBMED ID: 23570586

DOI: Mancante

Titolo: [Multicenter randomized controlled study of temozolomide versus semustine in the treatment of recurrent malignant glioma].

Autori: Sun J., Yang XJ., Yang SY.

Data di Pubblicazione: 2013-4-11

Abstract: The efficacy of TMZ for patients with recurrent GBM or AA is better than that of Me-CCNU. And TMZ has an acceptable safety profile and its adverse events are mostly mild.

Journal Title: Zhonghua yi xue za zhi

PUBMED ID: 23564811

DOI: Mancante

Titolo: Phase II study of bevacizumab and temsirolimus combination therapy for recurrent glioblastoma multiforme.

Autori: Lassen U., Sorensen M., Gaziel TB., Hasselbalch B., Poulsen HS.

Data di Pubblicazione: 2013-4-9

Abstract: Temsirolimus can be safely administered in combination with bevacizumab. This study failed to detect activity of such a combination in patients with progressive GBM beyond bevacizumab therapy.  
Journal Title: Anticancer research

PUBMED ID: 23549780  
DOI: doi.org/10.1007/s00066-012-0296-8  
Titolo: Quasi-VMAT in high-grade glioma radiation therapy.  
Autori: Fadda G., Massazza G., Zucca S., Durzu S., Meleddu G., Possanzini M., Farace P.  
Data di Pubblicazione: 2013-4-4  
Abstract: These findings suggest that qVMAT should be preferred to 3D-CRT for the treatment of high-grade gliomas. The qVMAT method could be applied in hospitals, for example, which have limited departmental resources and are not equipped with systems capable of VMAT delivery.  
Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 23536435  
DOI: doi.org/10.1158/1078-0432.CCR-13-0306  
Titolo: Phase I trial, pharmacokinetics, and pharmacodynamics of vandetanib and dasatinib in children with newly diagnosed diffuse intrinsic pontine glioma.  
Autori: Broniscer A., Baker SD., Wetmore C., Pai Panandiker AS., Huang J., D'Amico AM., Onar-Thomas A., Panetta JC., Chin TK., Merchant TE., Baker JN., Kaste SC., Gajjar A., Stewart CF.  
Data di Pubblicazione: 2013-3-29  
Abstract: The MTD of vandetanib and dasatinib in combination was 65 mg/m<sup>2</sup> for each drug. Other studies are underway to test dasatinib and other PDGFR inhibitors alone or in combination for this deadly cancer.  
Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 23508296  
DOI: doi.org/10.1007/s11060-013-1111-9  
Titolo: Outcome of infants and young children with newly diagnosed ependymoma treated on the "Head Start" III prospective clinical trial.  
Autori: Venkatramani R., Ji L., Lasky J., Haley K., Judkins A., Zhou S., Spoto R., Olshefski R., Garvin J., Tekautz T., Kennedy G., Rassekh SR., Moore T., Gardner S., Allen J., Shore R., Moertel C., Atlas M., Dhall G., Finlay J.  
Data di Pubblicazione: 2013-3-20  
Abstract: This study investigates the outcome of children <10 years old with newly-diagnosed ependymoma treated on the prospective multinational "Head Start" III clinical trial. Between April 2004 and July 2009, 19 children with newly-diagnosed ependymoma were enrolled. All children were to receive five induction chemotherapy cycles followed by one consolidation cycle of myeloablative chemotherapy and autologous hematopoietic cell rescue. Children between 6 and 10 years of age or with residual tumor prior to consolidation were to receive irradiation thereafter. Median age of 19 children (8 female) was 20 months at diagnosis. Median follow up was 44 months. The primary site was infratentorial in 11 and supratentorial in 8 patients. Gross total resection was achieved in 10 patients. After induction chemotherapy, all three supratentorial ependymoma patients with residual disease achieved a complete response (CR), while only one of six infratentorial patients with residual disease achieved CR. Three infratentorial patients developed progressive disease during induction chemotherapy. All four infratentorial patients with residual d

isease who underwent autologous hematopoietic cell transplant, failed to achieve CR. Four patients received focal irradiation following chemotherapy. The 3-year event free survival (EFS) and overall survival (OS) for supratentorial ependymoma were  $86 \pm 13\%$  and  $100\%$  respectively. The 3-year EFS and OS for infratentorial ependymoma were  $27 \pm 13\%$  and  $73 \pm 13\%$  respectively. The role of intensive induction and consolidation chemotherapy in deferring irradiation should be investigated further in children with supratentorial ependymoma with residual disease following surgery. This approach appears ineffective in children with infratentorial ependymoma in the absence of irradiation.

Journal Title: Journal of neuro-oncology

PUBMED ID: 23503634

DOI: doi.org/10.1007/s00381-013-2082-z

Titolo: Significance of radical resection for pilomyxoid astrocytoma of the cerebellum: a case report and review of the literature.

Autori: Okano A., Oya S., Fujisawa N., Tsuchiya T., Indo M., Nakamura T., Chang HS., Matsui T.

Data di Pubblicazione: 2013-3-19

Abstract: Although the prognosis of cerebellar PMAs remains unknown because of the paucity of cases, the relevant literature reports a more favorable outcome for cerebellar PMAs than for PMAs occurring at other locations. The results of this case study and a review of the relevant literature advocate radical resection, sometimes involving multiple surgeries, for cerebellar PMAs because gross total or near total resection is more feasible in the cerebellum than in other locations.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 23496909

DOI: doi.org/10.1186/1471-2407-13-106

Titolo: The prospective application of a hypoxic radiosensitizer, doranidazole to rat intracranial glioblastoma with blood brain barrier disruption.

Autori: Yasui H., Asanuma T., Kino J., Yamamori T., Meike S., Nagane M., Kubota N., Kuwabara M., Inanami O.

Data di Pubblicazione: 2013-3-19

Abstract: Our results revealed that BBB disruption in glioma enables BBB-impermeable radiosensitizers to penetrate and distribute in the target region. This study is the first to propose that in malignant glioma the administration of hydrophilic hypoxic radiosensitizers could be a potent strategy for improving the clinical outcome of radiotherapy without side effects.

Journal Title: BMC cancer

PUBMED ID: 23495876

DOI: doi.org/10.3171/2013.2.JNS121747

Titolo: Surgical management of multicentric diffuse low-grade gliomas: functional and oncological outcomes: clinical article.

Autori: Terakawa Y., Yordanova YN., Tate MC., Duffau H.

Data di Pubblicazione: 2013-3-19

Abstract: Multicentric DLGGs can be removed safely without inducing severe permanent neurological deficits. Interestingly, a single-stage resection of multiple lesions within different lobes may be performed if tumors are located in the same hemisphere. Therefore, the authors suggest considering surgery as the first therapeutic option for multicentric DLGGs, as in solitary DLGGs.

Journal Title: Journal of neurosurgery

PUBMED ID: 23486688

DOI: doi.org/10.1093/neuonc/not025

Titolo: STAT3 silencing inhibits glioma single cell infiltration and tumor growth.

Autori: Priester M., Copanaki E., Vafaizadeh V., Hensel S., Bernreuther C., Glatzel M., Seifert V., Groner B., Kögel D., Weissenberger J.

Data di Pubblicazione: 2013-3-15

Abstract: Our results show compelling evidence that STAT3 is a key driver of diffuse infiltration and glioma growth and might therefore represent a promising target for an anti-invasive therapy.

Journal Title: Neuro-oncology

PUBMED ID: 23453151

DOI: doi.org/10.1016/j.clineuro.2013.02.001

Titolo: Hypo-fractionated IMRT for patients with newly diagnosed glioblastoma multiforme: a 6 year single institutional experience.

Autori: Ciammella P., Galeandro M., D'Abbiero N., Podgornii A., Pisanello A., Botti A., Cagni E., Iori M., Iotti C.

Data di Pubblicazione: 2013-3-5

Abstract: The hypo-fractionated radiation therapy can be used for patients with GBM, resulting in favourable overall survival, low rates of toxicity and satisfying QoL. Future investigations are needed to determine the optimal fractionation for GBM.

Journal Title: Clinical neurology and neurosurgery

PUBMED ID: 23445331

DOI: doi.org/10.3109/02688697.2013.771136

Titolo: Diffusion tensor invasive phenotypes can predict progression-free survival in glioblastomas.

Autori: Mohsen LA., Shi V., Jena R., Gillard JH., Price SJ.

Data di Pubblicazione: 2013-3-1

Abstract: It is possible to identify three invasive phenotypes in GBMs using Diffusion tensor imaging, and these three phenotypes have different progression free survival. A minimal phenotype (20% of patients) predicts a greater delay to progression.

Journal Title: British journal of neurosurgery

PUBMED ID: 23444345

DOI: doi.org/10.1002/pbc.24496

Titolo: Intellectual and academic outcome following two chemotherapy regimens and radiotherapy for average-risk medulloblastoma: COG A9961.

Autori: Ris MD., Walsh K., Wallace D., Armstrong FD., Holmes E., Gajjar A., Zhou T., Packer RJ.

Data di Pubblicazione: 2013-2-28

Abstract: These results show progressive decline over several years post-treatment in standardized intellectual and academic scores. Despite recent improvements in therapies for these children, most notably a decrease dose of craniospinal radiation, they remain at risk. The pursuit of less toxic treatments, particularly for younger children, should continue. Neuropsychological surveillance should be routine at centers treating children with brain tumors.

Journal Title: Pediatric blood & cancer

PUBMED ID: 23436052

DOI: doi.org/10.3174/ajnr.A3421



Titolo: MR imaging assessment of tumor perfusion and 3D segmented volume at baseline, during treatment, and at tumor progression in children with newly diagnosed diffuse intrinsic pontine glioma.

Autori: Sedlacik J., Winchell A., Kocak M., Loeffler RB., Broniscer A., Hillenbrand CM.

Data di Pubblicazione: 2013-2-26

Abstract: Our results suggest that tumor perfusion may be a useful predictive marker for the assessment of treatment response and tumor progression in children with DIPG treated with both RT and vandetanib. The assessment of tumor perfusion yields valuable information about tumor microvascular status and its response to therapy, which may help better understand the biology of DIPGs and monitor novel treatment strategies in future clinical trials.

Journal Title: AJNR. American journal of neuroradiology

PUBMED ID: 23427031

DOI: doi.org/10.1055/s-0032-1333417

Titolo: Bilateral ptosis as initial presentation of gliomatosis cerebri: case report.

Autori: Kovanda T., Braca J., Prabhu V.

Data di Pubblicazione: 2013-2-22

Abstract: Gliomatosis cerebri is a rare, diffuse glioma of neuroepithelial origin involving more than two cerebral lobes. Clinical presentation of gliomatosis cerebri is variable and depends on the degree, extent, and location of cortical involvement. Signs and symptoms related to supratentorial cortical involvement predominate and the diagnosis is reached through a combination of clinical, radiographic, and histopathological evaluations. This is a report of a young man who presented with visual problems and bilateral ptosis, which were eventually attributed to gliomatosis cerebri. Standard radiation and chemotherapy were administered but the patient eventually succumbed to the disease. The unique clinical presentation is discussed in light of this rare neoplasm of the central nervous system.

Journal Title: Journal of neurological surgery. Part A, Central European neurosurgery

PUBMED ID: 23422903

DOI: doi.org/10.1227/NEU.0b013e31827d102e

Titolo: Anaplastic ependymoma with holocordal and intracranial meningeal carcinomatosis and holospinal bone metastases.

Autori: Pérez-Bovet J., Rimbau-Muñoz J., Martín-Ferrer S.

Data di Pubblicazione: 2013-2-21

Abstract: To our knowledge, there are no previous descriptions of ependymomas with this extensive leptomeningeal, spinal, intracranial, and extraneural dissemination at clinical onset. Bone metastases in spinal ependymoma have not been previously reported.

Journal Title: Neurosurgery

PUBMED ID: 23422478

DOI: Mancante

Titolo: Clinical experience of treatment of metastatic melanoma and solid tumours adopting a derivative of diphtheria toxin: cross-reacting material 197.

Autori: Fiorentini G., Banfi R., Dentico P., Moriconi S., Turrisi G., Pelagotti F., Rossi S., Montagnani F.

Data di Pubblicazione: 2013-2-21

Abstract: CRM197, injected subcutaneously at 5 mg, elicited a generic inflammatory response causing toxicity, and did not exert a significant degree of antitumor activity in patients with advanced melanoma and solid tumour.

Journal Title: In vivo (Athens, Greece)

PUBMED ID: 23417358

DOI: doi.org/10.1007/s11060-013-1072-z

Titolo: Early response evaluation for recurrent high grade gliomas treated with bevacizumab: a volumetric analysis using diffusion-weighted imaging.

Autori: Hwang EJ., Cha Y., Lee AL., Yun TJ., Kim TM., Park CK., Kim JH., Sohn CH., Park SH., Kim IH., Heo DS., Lee SH., Choi SH.

Data di Pubblicazione: 2013-2-19

Abstract: Bevacizumab is a novel treatment for the recurrent high-grade gliomas (rHGG). However, only a subset of the patients shows response to the bevacizumab treatment and the response evaluation using conventional criteria is difficult. The purpose of our study was to evaluate the early response for rHGG treated with bevacizumab using volumetric analysis of diffusion-weighted imaging (DWI). Twenty-nine patients who received bevacizumab therapy for rHGG were included in our study. All patients received a conventional MRI scan with DWI before and after the initial bevacizumab dose. For each MRI, we measured the total volume of the T2 hyperintense lesion (HT2) of the rHGG, the volume of foci with a lower ADC value than that of the normal cortex (LADC), and the proportion of LADC to HT2 (LADC/HT2). The changes in the HT2, LADC and LADC/HT2 after bevacizumab treatment were also determined. Thereafter, those volumetric data were compared to the progression free survival (PFS). After the analyses, we found a significant negative correlation between the PFS and the LADC for the post-bevacizumab ADC maps ( $r = -0.413$ ,  $P = 0.026$ ). The patients with an LADC of  $<2.5 \text{ cm}^3$  showed a longer PFS than those with an LADC of  $\geq 2.5 \text{ cm}^3$  (median = 135 vs. 91 days,  $P = 0.002$ ) on the post-bevacizumab ADC maps. A multiple linear regression analysis revealed that only the post-bevacizumab LADC was a significant predictor of the PFS ( $P = 0.026$ ). In conclusion, the post-bevacizumab LADC can be used for an early response evaluation and can predict the PFS for rHGG patients treated with bevacizumab.

Journal Title: Journal of neuro-oncology

PUBMED ID: 23400732

DOI: doi.org/10.1007/s00432-013-1390-8

Titolo: Bevacizumab plus irinotecan in recurrent or progressive malignant glioma: a multicenter study of the Anatolian Society of Medical Oncology (ASMO).

Autori: Demirci U., Tufan G., Aktas B., Balakan O., Alacacioglu A., Dane F., Engin H., Kaplan MA., Gunaydin Y., Ozdemir NY., Tugba Unek I., Karaca H., Akman T., Sonmez OU., Coskun U., Harputluoglu H., Sevinc A., Tonyali O., Buyukberber S., Benekli M.

Data di Pubblicazione: 2013-2-13

Abstract: Present study results were consistent with previous studies. In addition, we detected similar outcomes in grade III and IV glial tumors.

Journal Title: Journal of cancer research and clinical oncology

PUBMED ID: 23399039

DOI: doi.org/10.1016/j.ejrad.2012.12.018

Titolo: MRI assessment of relapsed glioblastoma during treatment with bevacizumab: volumetric measurement of enhanced and FLAIR lesions for evaluation of response and progression--a pilot study.

Autori: Pichler J., Pachinger C., Pelz M., Kleiser R.

Data di Pubblicazione: 2013-2-13

Abstract: In this pilot study the applied imaging estimates objectively tumor response and progression compared to the bi-dimensional measurement. The quantitative parameters are reproducible and also applicable for the diffuse infiltrating lesions.

Journal Title: European journal of radiology

PUBMED ID: 23377758

DOI: doi.org/10.1007/s00381-013-2042-7

Titolo: The efficacy of a biopsy of intrinsic brainstem lesions for decision making of the treatments.

Autori: Ogiwara H., Morota N.

Data di Pubblicazione: 2013-2-5

Abstract: Open biopsy of intrinsic brainstem lesions is considered to be safe and effective for selecting an appropriate course of therapy. Patients with intrinsic pontine lesions which extend beyond the pons or with localized enhancing portion seem to be benefited from the biopsy.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 23373800

DOI: doi.org/10.3171/2013.1.JNS121323

Titolo: Brainstem gangliogliomas: a retrospective series.

Autori: Zhang S., Wang X., Liu X., Ju Y., Hui X.

Data di Pubblicazione: 2013-2-5

Abstract: The diagnosis of brainstem ganglioglioma is of great importance given its favorable prognosis. The authors recommend the maximal safe resection followed by close observation without adjuvant therapy as the optimal treatment for this disease.

Journal Title: Journal of neurosurgery

PUBMED ID: 23363814

DOI: doi.org/10.1158/1078-0432.CCR-12-1707

Titolo: A phase I/II trial of pazopanib in combination with lapatinib in adult patients with relapsed malignant glioma.

Autori: Reardon DA., Groves MD., Wen PY., Nabors L., Mikkelsen T., Rosenfeld S., Raizer J., Barriuso J., McLendon RE., Suttle AB., Ma B., Curtis CM., Darnall MM., de Bono J.

Data di Pubblicazione: 2013-2-1

Abstract: The antitumor activity of this combination at the phase II dose tested was limited. Pharmacokinetic data indicated that exposure to lapatinib was subtherapeutic in the phase II evaluation. Evaluation of intratumoral drug delivery and activity may be essential for hypothesis-testing trials with targeted agents in malignant glioma.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 23357966

DOI: doi.org/10.1097/COC.0b013e31826b9903

Titolo: Histologically proven, low-grade brainstem gliomas in children: 30-year experience with long-term follow-up at Mayo Clinic.

Autori: Ahmed KA., Laack NN., Eckel LJ., Orme NM., Wetjen NM.

Data di Pubblicazione: 2013-1-30

Abstract: OS in this single institution retrospective study in pathologically proven BS-LGG with extensive follow-up displayed favorable long-term outcomes. Improved outcomes were associated with nondiffuse classification.

Journal Title: American journal of clinical oncology

PUBMED ID: 23348245

DOI: doi.org/10.1097/CAD.0b013e32835c7a47

Titolo: Long-term response in high-grade optic glioma treated with medically induced hypothyroidism and carboplatin: a case report and review of the literature.

Autori: Ashur-Fabian O., Blumenthal DT., Bakon M., Nass D., Davis PJ., Herbergs A.

Data di Pubblicazione: 2013-1-26

Abstract: Glioblastoma multiforme (GBM) is the most malignant and frequent brain tumor, with an aggressive growth pattern and poor prognosis despite best treatment modalities. Long-term survival of patients with GBM is rare. Optic glioma represents 0.6-1.2% of all brain tumors. Unlike low-grade optic gliomas in children, optic gliomas in adults are highly aggressive and death usually occurs in less than a year. Prolonged progression-free survival and survival rates have been reported in association with induced hypothyroidism in two clinical trials for recurrent GBM. We present the clinical, radiological, and pathological findings in a patient with inoperable GBM of the optic chiasm. Following failure of initial, standard radiation and temozolomide therapy, chemical hypothyroidism was induced using the antithyroid thioamide, propylthiouracil, followed by carboplatin chemotherapy. Initial thyroid stimulating hormone, free T4, and free T3 analysis was carried out and then monthly. This patient responded rapidly to treatment (clinically and with tumor regression within 4 weeks) on two separate occasions with an extended remission period (2.5 years) and prolonged overall survival (4.5 years). We report the successful long-term tumor response to medically induced chemical hypothyroidism in conjunction with carboplatin chemotherapy of an adult patient with grade IV GBM of the optic chiasm. These clinical observations find mechanistic support from the recent identification of potent mitogenic actions of the thyroid hormone, L-thyroxine, in malignant glioma through binding to a cognate thyroid hormone receptor on the  $\alpha\beta3$  integrin. Approaches to block its activity are now explored in preclinical studies.

Journal Title: Anti-cancer drugs

PUBMED ID: 23344784

DOI: doi.org/10.1007/s11307-013-0613-3

Titolo: 2-Deoxy-2-[18F]fluoro-D-glucose positron emission tomography demonstrates target inhibition with the potential to predict anti-tumour activity following treatment with the AKT inhibitor AZD5363.

Autori: Maynard J., Ricketts SA., Gendrin C., Dudley P., Davies BR.

Data di Pubblicazione: 2013-1-25

Abstract: We conclude that 18F-FDG PET is a promising pharmacodynamic biomarker of AKT pathway inhibition, with potential to predict and demonstrate anti-tumour activity. It is a biomarker that may stop ineffective drug schedules, helping to make early stop decisions and identify responding subsets of patients, resulting in improved clinical decision making both during drug development and patient management.

Journal Title: Molecular imaging and biology

PUBMED ID: 23341100

DOI: doi.org/10.1007/s11060-013-1058-x

Titolo: Gliomatosis cerebri: clinical characteristics, management, and outcomes.

Autori: Chen S., Tanaka S., Giannini C., Morris J., Yan ES., Buckner J., Lachance DH., Parney IF.

Data di Pubblicazione: 2013-1-24

Abstract: Gliomatosis cerebri is a rare diffusely infiltrating primary neoplastic glial process of the brain. Our objective is to review clinical presentation, management, and outcome in a large single institution series of gliomatosis cerebri patients. 54 consecutive gliomatosis cerebri cases presenting to Mayo Clinic Rochester between 1991 and 2008 were retrospectively reviewed.

ed. Inclusion criteria included involvement of at least three cerebral lobes, lack of a single discrete mass and pathological confirmation of diffuse glioma. Median overall survival (OS) was 18.5 months. Age, gender, presenting symptoms, and contrast enhancement did not correlate significantly with survival, though there was a trend toward decreased overall survival in patients above the median age of 46 years. Karnofsky performance score <70 was associated with poor OS (median 9.5 vs. 20.5 months,  $p = 0.02$ ). Higher histologic grade was associated with poor progression-free survival (PFS; median for WHO grades II, III, and IV: 21.5, 6.5, and 4 months;  $p = 0.03$ ) and OS (median 34, 15.5, and 8.5 months;  $p < 0.05$ ). Radiation therapy was strongly associated with better prognosis (PFS 16.5 vs. 4.5 months,  $p < 0.01$ ; OS 27.5 vs. 6.5,  $p < 0.01$ ), but chemotherapy was not. Gliomatosis cerebri patients have a poor prognosis. Lower KPS upon presentation and higher histologic grade predict decreased survival. Surgery's role is limited beyond biopsy for diagnostic purposes. Radiotherapy appears beneficial, although selection bias could be present in this retrospective study. Chemotherapy's value is not as clear but this must be interpreted with caution given variable treatment regimens in this series.

Journal Title: Journal of neuro-oncology

PUBMED ID: 23319493

DOI: doi.org/10.1530/ERC-12-0219

Titolo: Thyroid hormone, thyroid hormone receptors, and cancer: a clinical perspective.

Autori: Moeller LC., Führer D.

Data di Pubblicazione: 2013-1-16

Abstract: Thyroid hormones (THs) may play a role in diseases other than hyper- and hypothyroidism. Several lines of evidence suggest tumor-promoting effects of TH and TH receptors. They are possibly mediated by phosphatidylinositol-3-kinase and MAPK and involve among others stimulation of angiogenesis via  $\alpha v \beta 3$ . Thus, an increased risk for colon, lung, prostate, and breast cancer with lower TSH has been demonstrated in epidemiological studies, even suggesting a TH dose effect on cancer occurrence. Furthermore, higher TH levels were associated with an advanced clinical stage of breast and prostate cancer. In rodent models, TH stimulated growth and metastasis of tumor transplants, whereas hypothyroidism had opposite effects. In clinical studies of glioblastoma and head and neck cancer, hypothyroid patients showed longer survival than euthyroid patients. Also, patients with renal cell cancer that were treated with the tyrosine kinase inhibitor sunitinib and developed hypothyroidism in due course showed significantly longer survival than patients that remained euthyroid. Development of hypothyroidism was an independent predictor for survival in two studies. Yet, it is still possible that hypothyroidism is only a surrogate marker for treatment efficacy and does not positively influence treatment outcome by itself. Future cancer treatment studies, especially with substances that can induce hypothyroidism, should therefore be designed in a way that allows for an analysis of thyroid function status and its contribution on treatment outcome.

Journal Title: Endocrine-related cancer

PUBMED ID: 23314822

DOI: doi.org/10.1007/s11060-013-1044-3

Titolo: Re-irradiation with and without bevacizumab as salvage therapy for recurrent or progressive high-grade gliomas.

Autori: Hunsberger T., Brüggé D., Putorä PM., Weder P., Weber J., Plasswilm L.

Data di Pubblicazione: 2013-1-15

Abstract: The optimal treatment for recurrent high-grade gliomas is unknown and a standard of care does not exist. Re-irradiation with concomitant bevac

izumab represents an option. Retrospectively, we analyzed a cohort of heavily pretreated patients (n = 14) with relapsing HGGs who underwent re-irradiation with conventional 3D-conformal or intensified modulated radiotherapy (IMRT). Ten of them received re-irradiation in combination with bevacizumab. The study population consisted of eight GBMs and six anaplastic gliomas. All patients had previously undergone irradiation for first-line therapy, including seven patients with radiochemotherapy with temozolomide. Patients without contraindications started with two infusions of bevacizumab (10 mg/kg of body weight every other week) prior to re-irradiation and continued through re-irradiation until progression. The median patient age was 45 years with a median Karnofsky performance scale of 70. The median dose of re-irradiation was 41.6 Gy [39-55 Gy]. The median physical cumulative radiation dose was 101.6 Gy [65-110.4 Gy]. The median PFS from re-irradiation was 5.1 months [1.6-17.4] based on clinical and RANO criteria. Median OS from re-irradiation was 9.0 months [6.4-17.8]. We detected radionecrosis due to advanced imaging in one patient. Other toxicities were expected and attributable well known side effects of bevacizumab. This retrospective study provides additional feasibility and safety data of conventional 3D-conformal re-irradiation and IMRT in combination with bevacizumab in relapsing high-grade gliomas.

Journal Title: Journal of neuro-oncology

PUBMED ID: 23302906

DOI: doi.org/10.1177/107327481302000107

Titolo: Current status of immunotherapy and gene therapy for high-grade gliomas.

Autori: Marsh JC., Goldfarb J., Shafman TD., Diaz AZ.

Data di Pubblicazione: 2013-1-11

Abstract: Although phase III data are needed before immunologic therapies can be widely implemented into clinical practice, the existing phase I and phase II data suggest that these therapies can produce meaningful and sometimes durable responses in patients with glioblastoma multiforme with mild toxicity compared with other existing therapies.

Journal Title: Cancer control : journal of the Moffitt Cancer Center

PUBMED ID: 23299464

DOI: doi.org/10.1007/s11060-013-1048-z

Titolo: "One week on-one week off": efficacy and side effects of dose-intensified temozolomide chemotherapy: experiences of a single center.

Autori: Galldi N., Berhorn T., Blau T., Dunkl V., Fink GR., Schroeter M.

Data di Pubblicazione: 2013-1-10

Abstract: To evaluate in a single center retrospectively the efficacy and tolerability of a weekly regimen, which alternates temozolomide (TMZ) in patients with recurrent or progressive high-grade glioma (HGG). From January 2005 until June 2011, 54 patients with recurrent or progressive HGG were treated with TMZ 150 mg/m<sup>2</sup>/day on days 1-7 and 15-21 of a 28-day cycle ("one week on-one week off" scheme; TMZ 7/14) with individual dose adjustment depending on toxicity. The majority of patients (n = 48, 89 %) was treated at first tumor recurrence or progression. All patients had received prior radiotherapy with or without concomitantly administered TMZ and, optionally, adjuvant chemotherapy. After initiation of TMZ 7/14, MRI was obtained every 8-12 weeks. Tumor response or progression was assessed according to Macdonald criteria. Blood examinations were performed weekly. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE; version 3.0). A total of 434 treatment weeks with TMZ 7/14 were delivered. The median number of treatment weeks was 7 (range, 1-41 weeks). No grade 4 hematological toxicity and no opportunistic infections occurred. Patients with neutropenia were not observed. Two patients developed grade 3 and 4 patients grade 2 leukocytopenia. Thrombocytopenia grade 3 and grade 2 occurred in 4 patients and 6 patients.

ts, respectively. The progression-free survival (PFS) rate at 6 months was 43 %. Median PFS from treatment initiation was 18 weeks (95 % CI, 14-22 weeks) and median overall survival (OS) was 37 weeks (95 % CI, 31-42 weeks). The rates for PFS and OS at 1 year were 24 and 28 %, respectively. Our data suggest that treatment with TMZ 7/14 is safe and effective in patients with recurrent or progressive HGG.

Journal Title: Journal of neuro-oncology

PUBMED ID: 23296323

DOI: doi.org/10.1007/s00381-012-2013-4

Titolo: Response to bevacizumab, irinotecan, and temozolomide in children with relapsed medulloblastoma: a multi-institutional experience.

Autori: Aguilera D., Mazewski C., Fangusaro J., MacDonald TJ., McNall-Knapp RY., Hayes LL., Kim S., Castellino RC.

Data di Pubblicazione: 2013-1-9

Abstract: The combination of bevacizumab and irinotecan, with or without temozolomide, produces objective responses with minimal toxicity in children with recurrent medulloblastoma. Prospective clinical trials are needed to evaluate the efficacy of this strategy.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 23293772

DOI: doi.org/10.3389/fonc.2012.00205

Titolo: Diffuse intrinsic pontine glioma: poised for progress.

Autori: Warren KE.

Data di Pubblicazione: 2013-1-8

Abstract: Diffuse intrinsic pontine gliomas (DIPGs) are amongst the most challenging tumors to treat. Surgery is not an option, the effects of radiation therapy are temporary, and no chemotherapeutic agent has demonstrated significant efficacy. Numerous clinical trials of new agents and novel therapeutic approaches have been performed over the course of several decades in efforts to improve the outcome of children with DIPG, yet without success. The diagnosis of DIPG is based on radiographic findings in the setting of a typical clinical presentation, and tissue is not routinely obtained as the standard of care. The paradigm for treating children with these tumors has been based on that for supratentorial high-grade gliomas in adults as the biology of these lesions were presumed to be similar. However, recent pivotal studies demonstrate that DIPGs appear to be their own entity. Simply identifying this fact releases a number of constraints and opens opportunities for biologic investigation of these lesions, setting the stage to move forward in identifying DIPG-specific treatments. This review will summarize the current state of knowledge of DIPG, discuss obstacles to therapy, and summarize results of recent biologic studies.

Journal Title: Frontiers in oncology

PUBMED ID: 23292205

DOI: doi.org/10.1007/s00415-012-6812-z

Titolo: A phase I study of temozolomide and lapatinib combination in patients with recurrent high-grade gliomas.

Autori: Karavasilis V., Kotoula V., Pentheroudakis G., Televantou D., Lambaki S., Chrisafi S., Bobos M., Fountzilas G.

Data di Pubblicazione: 2013-1-8

Abstract: We undertook this phase I study to investigate the feasibility of the combination of temozolomide (TMZ) and lapatinib (LP) and to define the maximum tolerated dose (MTD) of LP in patients with relapsed high-grade gliomas. Eligible patients were enrolled in this dose escalation study of LP. TMZ

was administered at a fixed dose of 200 mg/m<sup>2</sup> d1-d5 every 28 days. Starting dose of LP was set at 1,000 mg daily continuously, escalated by 250 mg in cohorts of minimum three patients. Translational research investigations were also undertaken in available biopsy material. Between January 2009 and December 2010, 16 patients were entered into the study at three LP levels: 1,000 mg sid (11 patients), 1,250 mg sid (4 patients) and 1,500 mg sid (1 patient). A total of 55 cycles had been delivered. Fourteen patients had stopped treatment because of disease progression, and two because of toxicity. Three patients received 10, 11 and 17 cycles of treatment. Dose-limiting hematologic toxicity was observed in 2 patients at the second LP dose level of 1,250 mg sid. MTD was defined at LP 1,000 mg sid. Median progression-free survival (PFS) and survival were 2.4 and 5.9 months, respectively. EGFR amplification and EGFRvIII expression were not related to PFS. Combination of TMZ and LP is feasible with manageable toxicity. The activity of this combination in patients with recurrent glioblastoma multiforme is further investigated in a recently initiated phase II trial.

Journal Title: Journal of neurology

PUBMED ID: 23289916

DOI: doi.org/10.3171/2012.11.PEDS12317

Titolo: Management and outcome of focal low-grade brainstem tumors in pediatric patients: the St. Jude experience.

Autori: Klimo P., Pai Panandiker AS., Thompson CJ., Boop FA., Qaddoumi I., Gajjar A., Armstrong GT., Ellison DW., Kun LE., Ogg RJ., Sanford RA.

Data di Pubblicazione: 2013-1-8

Abstract: Surgery suffices in many children with low-grade focal brainstem gliomas. Radiation treatment is often reserved for disease progression but offers comparable disease control following biopsy. In the authors' experience, combining an assessment of clinical course, imaging, and tumor biopsy yields a reasonable model for managing children with focal brainstem tumors.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 23259383

DOI: Mancante

Titolo: [Personalized peptide vaccination].

Autori: Itoh K., Takahashi R., Yoshitomi M., Terasaki M., Noguchi M.

Data di Pubblicazione: 2012-12-25

Abstract: We conducted personalized peptide vaccination (PPV) for various types of advanced cancers in the past 10 years. A maximum of four HLA-matched peptides, which were selected based on the pre-existing host immunity before vaccination, were subcutaneously administered at PPV trials. Randomized phase II trial for patients with castration resistant prostate cancer showed the favorite clinical responses in the PPV group. PPV was also conducted for recurrent or progressive glioblastoma multiforme patients with median overall survival of 10.6 months, resulting in the initiation of randomized phase III clinical trial. A randomized phase III trial is essential to prove clinical benefits of PPV.

Journal Title: Nihon rinsho. Japanese journal of clinical medicine

PUBMED ID: 23259381

DOI: Mancante

Titolo: [WT1-targeting cancer vaccine].

Autori: Sugiyama H.

Data di Pubblicazione: 2012-12-25

Abstract: Wilms' tumor gene WT1 encodes a transcription factor and functions as an oncogene. WT1 gene product WT1 protein is a promising par-tumor-associated antigen. WT1 peptide-based immunotherapy has been performing for more t



han six hundred patients with leukemias and various types of solid tumors. This immunotherapy is safe and has clinical benefit especially for leukemia, glioblastoma multiforme, advanced pancreatic cancer, and ovarian cancer. As a new strategy for cancer treatment, it should be recommended to initiate immunotherapy that had a potential of eradication of cancer stem cells before surgery, chemo- and radio-therapy.

Journal Title: Nihon rinsho. Japanese journal of clinical medicine

PUBMED ID: 23249962

DOI: doi.org/10.1097/MPH.0b013e318279aed8

Titolo: Prolonged survival after treatment of diffuse intrinsic pontine glioma with radiation, temozolamide, and bevacizumab: report of 2 cases.

Autori: Aguilera DG., Mazewski C., Hayes L., Jordan C., Esiashivilli N., Janans A., Macdonald TJ.

Data di Pubblicazione: 2012-12-20

Abstract: A clinical trial in an expanded cohort is warranted to determine the toxicity and evaluate response.

Journal Title: Journal of pediatric hematology/oncology

PUBMED ID: 23240851

DOI: doi.org/10.3171/2012.10.PEDS12142

Titolo: Convection-enhanced delivery of topotecan into diffuse intrinsic brainstem tumors in children.

Autori: Anderson RC., Kennedy B., Yanes CL., Garvin J., Needle M., Canoll P., Feldstein NA., Bruce JN.

Data di Pubblicazione: 2012-12-18

Abstract: Convection-enhanced delivery (CED) for the treatment of malignant gliomas is a technique that can deliver chemotherapeutic agents directly into the tumor and the surrounding interstitium through sustained, low-grade positive-pressure infusion. This allows for high local concentrations of drug within the tumor while minimizing systemic levels that often lead to dose-limiting toxicity. Diffuse intrinsic pontine gliomas (DIPGs) are universally fatal childhood tumors for which there is currently no effective treatment. In this report the authors describe CED of the topoisomerase inhibitor topotecan for the treatment of DIPG in 2 children. As part of a pilot feasibility study, the authors treated 2 pediatric patients with DIPG. Stereotactic biopsy with frozen section confirmation of glial tumor was followed by placement of bilateral catheters for CED of topotecan during the same procedure. The first patient underwent CED 210 days after initial diagnosis, after radiation therapy and at the time of tumor recurrence, with a total dose of 0.403 mg in 6.04 ml over 100 hours. Her Karnofsky Performance Status (KPS) score was 60 before CED and 50 posttreatment. Serial MRI initially demonstrated a modest reduction in tumor size and edema, but the tumor progressed and the patient died 49 days after treatment. The second patient was treated 24 days after the initial diagnosis prior to radiation with a total dose of 0.284 mg in 5.30 ml over 100 hours. Her KPS score was 70 before CED and 50 posttreatment. Serial MRI similarly demonstrated an initial modest reduction in tumor size. The patient subsequently underwent fractionated radiation therapy, but the tumor progressed and she died 120 days after treatment. Topotecan delivered by prolonged CED into the brainstem in children with DIPG is technically feasible. In both patients, high infusion rates ( $> 0.12$  ml/hr) and high infusion volumes ( $> 2.8$  ml) resulted in new neurological deficits and reduction in the KPS score, but lower infusion rates ( $< 0.04$  ml/hr) were well tolerated. While serial MRI showed moderate treatment effect, CED did not prolong survival in these 2 patients. More studies are needed to improve patient selection and determine the optimal flow rates for CED of chemotherapeutic agents into DIPG to maximize safety and efficacy. Clinical trial registration no.: NCT00324844.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 23240849

DOI: doi.org/10.3171/2012.11.PEDS12234

Titolo: Malignant glioma with angiocentric features.

Autori: Lu JQ., Patel S., Wilson BA., Pugh J., Mehta V.

Data di Pubblicazione: 2012-12-18

Abstract: Angiocentric glioma is a recently recognized benign brain tumor with unknown histogenesis. Most of these tumors are mitotically low in activity in accord with their benign clinical course. However, increased mitotic activity has been noted in several cases, one of which had an ultimately fatal outcome. Here, the authors present a tumor showing angiocentric glioma and glioblastoma-like features, with recurrence of the lower-grade component after radiotherapy. A 15-year-old boy presented with a 3-month history of progressive left-sided weakness and headache. Magnetic resonance imaging showed a large heterogeneous mass in the right frontal lobe, with mild post-Gd enhancement. A gross-total resection was obtained. Histopathological examination of the resected tissue revealed a tumor with 2 distinct appearances: 1) a mildly to moderately cellular infiltrating tumor with angiocentric glioma characteristics, and 2) a markedly cellular glioblastoma-like tissue with necrosis and microvascular proliferation. The patient received a course of postoperative radiotherapy to 59.4 Gy in 33 fractions administered over the course of 6.5 weeks, but his tumor recurred 4 months after resection. A second resection was then performed. The recurrent tumor exhibited radiation-induced changes and persistent characteristics of angiocentric glioma, but it had fewer malignant features; the mitotic activity was lower, and there was no necrosis or microvascular proliferation. The findings in this case, along with those in several previously reported cases, suggest that angiocentric gliomas may have a malignant variant or malignant transformation. Angiocentric gliomas with malignant features tend to recur, for which surgical intervention followed by radiotherapy and chemotherapy should be offered as a therapeutic option.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 23216891

DOI: doi.org/10.1186/1471-2164-13-686

Titolo: A REST derived gene signature stratifies glioblastomas into chemotherapy resistant and responsive disease.

Autori: Wagoner MP., Roopra A.

Data di Pubblicazione: 2012-12-11

Abstract: This report is the first to describe a REST gene signature that predicts response to multiple rounds of chemotherapy, the mainline therapy for this disease. The REST gene signature may have important clinical implications for the treatment of glioblastoma.

Journal Title: BMC genomics

PUBMED ID: 23207974

DOI: doi.org/10.1007/s00381-012-1970-y

Titolo: Pilocytic astrocytoma with leptomeningeal dissemination.

Autori: Bian SX., McAleer MF., Vats TS., Mahajan A., Grosshans DR.

Data di Pubblicazione: 2012-12-5

Abstract: Treatment of disseminated PA is frequently multi-modal, including surgical resection, chemotherapy, and radiation therapy. On the basis of early clinical data, extended-field radiation therapy is a viable option for treating disseminated PA.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 23204544

DOI: doi.org/10.1148/radiol.12111472

Titolo: Pseudoprogession of glioblastoma after chemo- and radiation therapy : diagnosis by using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging with ferumoxytol versus gadoteridol and correlation with survival.

Autori: Gahramanov S., Muldoon LL., Varallyay CG., Li X., Kraemer DF., Fu R., Hamilton BE., Rooney WD., Neuwelt EA.

Data di Pubblicazione: 2012-12-4

Abstract: Ferumoxytol as a blood pool agent facilitates differentiation between tumor progression and pseudoprogession, appears to be a good prognostic biomarker, and unlike gadoteridol, does not require contrast agent leakage correction.

Journal Title: Radiology

PUBMED ID: 23176331

DOI: doi.org/10.3171/2012.10.JNS112268

Titolo: Presentation, management, and outcome of newly diagnosed glioblastoma in elderly patients.

Autori: Tanaka S., Meyer FB., Buckner JC., Uhm JH., Yan ES., Parney IF.

Data di Pubblicazione: 2012-11-27

Abstract: The prognosis for GBM worsens with increasing age in elderly patients. With important risks, resection and adjuvant treatment are associated with prolonged survival. Although selection bias cannot be excluded in this retrospective study, advanced age alone should not necessarily preclude optimal resection followed by adjuvant radiochemotherapy.

Journal Title: Journal of neurosurgery

PUBMED ID: 23140402

DOI: doi.org/10.1186/1748-717X-7-189

Titolo: First experiences in treatment of low-grade glioma grade I and II with proton therapy.

Autori: Hauswald H., Rieken S., Ecker S., Kessel KA., Herfarth K., Debus J., Combs SE.

Data di Pubblicazione: 2012-11-13

Abstract: Regarding early side effects, mild alopecia was the predominant finding. The rate of alopecia seems to be due to large treatment volumes as well as the anatomical locations of the target volumes and might be avoided by using multiple beams and the gantry in the future. Further evaluations including neuropsychological testing are in preparation.

Journal Title: Radiation oncology (London, England)

PUBMED ID: 23138021

DOI: doi.org/10.1258/ar.2012.120525

Titolo: Can MRI-derived factors predict the survival in glioblastoma patients treated with postoperative chemoradiation therapy?

Autori: Nakamura H., Murakami R., Hirai T., Kitajima M., Yamashita Y.

Data di Pubblicazione: 2012-11-10

Abstract: The minimum ADC on pretreatment DW-MRI and gross residual tumor on early postoperative MRI can predict the survival in GBM patients treated with postoperative chemo-RT.

Journal Title: Acta radiologica (Stockholm, Sweden : 1987)

PUBMED ID: 23136223

DOI: doi.org/10.1093/neuonc/nos273

Titolo: Standards of care for treatment of recurrent glioblastoma--are we there yet?

Autori: Weller M., Cloughesy T., Perry JR., Wick W.

Data di Pubblicazione: 2012-11-9

Abstract: Newly diagnosed glioblastoma is now commonly treated with surgery, if feasible, or biopsy, followed by radiation plus concomitant and adjuvant temozolomide. The treatment of recurrent glioblastoma continues to be a moving target as new therapeutic principles enrich the standards of care for newly diagnosed disease. We reviewed PubMed and American Society of Clinical Oncology abstracts from January 2006 to January 2012 to identify clinical trials investigating the treatment of recurrent or progressive glioblastoma with nitrosoureas, temozolomide, bevacizumab, and/or combinations of these agents. At recurrence, a minority of patients are eligible for second surgery or reirradiation, based on appropriate patient selection. In temozolomide-pretreated patients, progression-free survival rates at 6 months of 20%-30% may be achieved either with nitrosoureas, temozolomide in various dosing regimens, or bevacizumab. Combination regimens among these agents or with other drugs have not produced evidence for superior activity but commonly produce more toxicity. More research is needed to better define patient profiles that predict benefit from the limited therapeutic options available after the current standard of care has failed.

Journal Title: Neuro-oncology

PUBMED ID: 23134812

DOI: doi.org/10.1186/1471-2407-12-508

Titolo: Treatment of medulloblastoma using an oncolytic measles virus encoding the thyroïdal sodium iodide symporter shows enhanced efficacy with radioiodine.

Autori: Hutzen B., Pierson CR., Russell SJ., Galanis E., Raffel C., Studebaker AW.

Data di Pubblicazione: 2012-11-9

Abstract: These data suggest MV-NIS plus radioiodine may be a potentially useful therapy for the treatment of medulloblastoma.

Journal Title: BMC cancer

PUBMED ID: 23129347

DOI: doi.org/10.1007/s11060-012-0999-9

Titolo: Hypofractionated stereotactic radiotherapy and continuous low-dose temozolomide in patients with recurrent or progressive malignant gliomas.

Autori: Minniti G., Scaringi C., De Sanctis V., Lanzetta G., Falco T., Di Stefano D., Esposito V., Enrici RM.

Data di Pubblicazione: 2012-11-7

Abstract: To evaluate the efficacy of reirradiation and systemic chemotherapy as salvage treatment in patients with recurrent malignant glioma. Between May 2006 and December 2011, 54 patients with recurrent malignant glioma received hypofractionated stereotactic radiotherapy (HSRT) plus systemic therapy at University of Rome Sapienza, Sant' Andrea Hospital. All patients had Karnofsky performance score  $\geq 60$  and were previously treated with standard conformal RT (60 Gy) with concomitant and adjuvant temozolomide (TMZ) up to 12 cycles. Thirty-eight patients had a GBM and 16 patients had a grade 3 glioma. The median time interval between primary RT and reirradiation was 15.5 months. At the time of recurrence all patients received HSRT (30 Gy in 6-Gy fractions) plus concomitant TMZ (75 mg/m<sup>2</sup>/day) followed by continuous TMZ at 50 mg/m<sup>2</sup> everyday up to 1 year or until progression. Median overall survival after HSRT was 12.4 months, and the 12- and 24-month survival rates were 53 and 16 %, respectively. The median progression-free survival (PFS) was 6 months, and the 12- and 24-month PFS rates were 24 and 10 %, respectively. KPS

>70 ( $P = 0.04$ ) and grade 3 glioma were independent favourable prognostic factors for survival. In general chemoradiation regimen was well tolerated with relatively low treatment-related toxicity. HSRT plus concomitant TMZ followed by continuous dose-intense TMZ is a feasible treatment option associated with survival benefits and low risk of complications in selected patients with recurrent malignant glioma. The potential advantages of combined chemoradiation schedules in patients with recurrent malignant gliomas need to be explored in future studies.

Journal Title: Journal of neuro-oncology

PUBMED ID: 23118709

DOI: doi.org/10.2147/CE.S23244

Titolo: Polifeprosan 20, 3.85% carmustine slow-release wafer in malignant glioma: evidence for role in era of standard adjuvant temozolomide.

Autori: Kleinberg L.

Data di Pubblicazione: 2012-11-3

Abstract: The Polifeprosan 20 with carmustine (BCNU, bis-chloroethylnitrosourea, Gliadel®) polymer implant wafer is a biodegradable compound containing 3.85% carmustine which slowly degrades to release carmustine and protects it from exposure to water with resultant hydrolysis until the time of release. The carmustine implant wafer was demonstrated to improve survival in blinded placebo-controlled trials in selected patients with newly diagnosed or recurrent malignant glioma, with little increased risk of adverse events. Based on these trials and other supporting data, US and European regulatory authorities granted approval for its use in recurrent and newly diagnosed malignant glioma, and it remains the only approved local treatment. The preclinical and clinical data suggest that it is optimally utilized primarily in the proportion of patients who may have total or near total removal of gross tumor. The aim of this work was to review the evidence for the use of carmustine implants in the management of malignant astrocytoma (World Health Organization grades III and IV), including newly diagnosed and recurrent disease, especially in the setting of a standard of care that has changed since the randomized trials were completed. Therapy has evolved such that patients now generally receive temozolomide chemotherapy during and after radiotherapy treatment. For patients undergoing repeat resection for malignant glioma, a randomized, blinded, placebo-controlled trial demonstrated a median survival for 110 patients who received carmustine polymers of 31 weeks compared with 23 weeks for 122 patients who only received placebo polymers. The benefit achieved statistical significance only on analysis adjusting for prognostic factors rather than for the randomized groups as a whole (hazard ratio = 0.67,  $P = 0.006$ ). A blinded, placebo-controlled trial has also been performed for carmustine implant placement in newly diagnosed patients prior to standard radiotherapy. Median survival was improved from 11.6 to 13.9 months ( $P = 0.03$ ), with a 29% reduction in the risk of death. When patients with glioblastoma multiforme alone were analyzed, the median survival improved from 11.4 to 13.5 months, but this improvement was not statistically significant. When a Cox's proportional hazard model was utilized to account for other potential prognostic factors, there was a significant 31% reduction in the risk of death ( $P = 0.04$ ) in this subgroup. Data from other small reports support these results and confirm that the incidence of adverse events does not appear to be increased meaningfully. Given the poor prognosis without possibility of cure, these benefits from a treatment with a favorable safety profile were considered meaningful. There is randomized evidence to support the use of carmustine wafers placed during resection of recurrent disease. Therefore, although there is limited specific evidence, this treatment is likely to be efficacious in an environment when nearly all patients receive temozolomide as part of initial management. Given that half of the patients in the randomized trial assessing the value of carmustine implants in recurrent disease had received prior chemotherapy, it is likely that this remains a valuable treatment at t

he time of repeat resection, even after temozolomide. There are data from multiple reports to support safety. Although there is randomized evidence to support the use of this therapy in newly diagnosed patients who will receive radiotherapy alone, it is now standard to administer both adjuvant temozolomide and radiotherapy. There are survival outcome reports for small cohorts of patients receiving temozolomide with radiotherapy, but this information is not sufficient to support firm recommendations. Based on the rationale and evidence of safety, this approach appears to be a reasonable option as more information is acquired. Available data support the safety of using carmustine wafers in this circumstance, although special attention to surgical guidelines for implanting the wafers is warranted.

Journal Title: Core evidence

PUBMED ID: 23095831

DOI: doi.org/10.1093/neuonc/nos199

Titolo: Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments.

Autori: Rudà R., Bello L., Duffau H., Soffietti R.

Data di Pubblicazione: 2012-10-26

Abstract: Seizures represent a common symptom in low-grade gliomas; when uncontrolled, they significantly contribute to patient morbidity and negatively impact quality of life. Tumor location and histology influence the risk for epilepsy. The pathogenesis of tumor-related epilepsy is multifactorial and may differ among tumor histologies (glioneuronal tumors vs diffuse grade II gliomas). Gross total resection is the strongest predictor of seizure freedom in addition to clinical factors, such as preoperative seizure duration, type, and control with antiepileptic drugs (AEDs). Epilepsy surgery may improve seizure control. Radiotherapy and chemotherapy with alkylating agents (procarbazine + CCNU+ vincristine, temozolomide) are effective in reducing the frequency of seizures in patients with pharmacoresistant epilepsy. Newer AEDs (levetiracetam, topiramate, lacosamide) seem to be better tolerated than the old AEDs (phenobarbital, phenytoin, carbamazepine), but there is lack of evidence regarding their superiority in terms of efficacy.

Journal Title: Neuro-oncology

PUBMED ID: 25057864

DOI: doi.org/10.2217/cns.12.15

Titolo: Pediatric diffuse intrinsic pontine glioma: can optimism replace pessimism?

Autori: Hargrave D.

Data di Pubblicazione: 2014-7-25

Abstract: Pediatric diffuse intrinsic pontine glioma (DIPG) has a dismal prognosis that has not seen a change in outcome despite multiple clinical trials. Possible reasons for failure to make progress in this aggressive childhood brain tumor include: poor understanding of the underlying molecular biology due to lack of access to tumor material; absence of accurate and relevant DIPG preclinical models for drug development; ill-defined therapeutic targets for novel agents; and inadequate drug delivery to the brainstem. This review will demonstrate that systematic studies to identify solutions for each of these barriers is starting to deliver progress that can turn pessimism to optimism in DIPG.

Journal Title: CNS oncology

PUBMED ID: 23092875

DOI: doi.org/10.1158/1078-0432.CCR-12-1501

Titolo: Do imaging biomarkers relate to outcome in patients treated with VEGF inhibitors?

Autori: O'Connor JP., Jayson GC.

Data di Pubblicazione: 2012-10-25

Abstract: The management of solid tumors has been transformed by the advent of VEGF pathway inhibitors. Early clinical evaluation of these drugs has used pharmacodynamic biomarkers derived from advanced imaging such as dynamic MRI, computed tomography (CT), and ultrasound to establish proof of principle. We have reviewed published studies that used these imaging techniques to determine whether the same biomarkers relate to survival in renal, hepatocellular, and brain tumors in patients treated with VEGF inhibitors. Data show that in renal cancer, pretreatment measurements of K(trans) and early pharmacodynamic reduction in tumor enhancement and density have prognostic significance in patients treated with VEGF inhibitors. A weaker, but significant, relationship is seen with subtle early size change (10% in one dimension) and survival. Data from high-grade glioma suggest that pretreatment fractional blood volume and K(trans) were prognostic of overall survival. However, lack of control data with other therapies prevents assessment of the predictive nature of these biomarkers, and such studies are urgently required.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 23077873

DOI: Mancante

Titolo: [Features of brain stem tumors in children].

Autori: Ciobanu A., Miron I., Tansanu I.

Data di Pubblicazione: 2012-10-20

Abstract: Brain stem tumors are still difficult to investigate, and the results on their long- and medium-term survival remain uncertain.

Journal Title: Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi

PUBMED ID: 23056240

DOI: doi.org/10.1371/journal.pone.0046104

Titolo: Tumor endothelial inflammation predicts clinical outcome in diverse human cancers.

Autori: Pitroda SP., Zhou T., Sweis RF., Filippo M., Labay E., Beckett MA., Mauceri HJ., Liang H., Darga TE., Perakis S., Khan SA., Sutton HG., Zhang W., Khodarev NN., Garcia JG., Weichselbaum RR.

Data di Pubblicazione: 2012-10-12

Abstract: This study provides the first prognostic cancer gene signature derived from an experimental model of tumor-associated endothelial inflammation. These findings support the notion that activation of inflammatory pathways in non-malignant tumor-infiltrating endothelial cells contributes to tumor growth and progression in multiple human cancers. Importantly, these results identify endothelial-derived factors that could serve as potential targets for therapy in diverse human cancers.

Journal Title: PloS one

PUBMED ID: 23056179

DOI: doi.org/10.1371/journal.pone.0044372

Titolo: Evaluation of tyrosine kinase inhibitor combinations for glioblastoma therapy.

Autori: Joshi AD., Loilome W., Siu IM., Tyler B., Gallia GL., Riggins GJ.

Data di Pubblicazione: 2012-10-12

Abstract: Glioblastoma multiforme (GBM) is the most common intracranial cancer but despite recent advances in therapy the overall survival remains about 20 months. Whole genome exon sequencing studies implicate mutations in the receptor tyrosine kinase pathways (RTK) for driving tumor growth in over 80%

of GBMs. In spite of various RTKs being mutated or altered in the majority of GBMs, clinical studies have not been able to demonstrate efficacy of molecular targeted therapies using tyrosine kinase inhibitors in GBMs. Activation of multiple downstream signaling pathways has been implicated as a possible means by which inhibition of a single RTK has been ineffective in GBM. In this study, we sought a combination of approved drugs that would inhibit in vitro and in vivo growth of GBM oncospheres. A combination consisting of gefitinib and sunitinib acted synergistically in inhibiting growth of GBM oncospheres in vitro. Sunitinib was the only RTK inhibitor that could induce apoptosis in GBM cells. However, the in vivo efficacy testing of the gefitinib and sunitinib combination in an EGFR amplified/PTEN wild type GBM xenograft model revealed that gefitinib alone could significantly improve survival in animals whereas sunitinib did not show any survival benefit. Subsequent testing of the same drug combination in a different syngeneic glioma model that lacked EGFR amplification but was more susceptible to sunitinib in vitro demonstrated no survival benefit when treated with gefitinib or sunitinib or the gefitinib and sunitinib combination. Although a modest survival benefit was obtained in one of two animal models with EGFR amplification due to gefitinib alone, the addition of sunitinib, to test our best in vitro combination therapy, did not translate to any additional in vivo benefit. Improved targeted therapies, with drug properties favorable to intracranial tumors, are likely required to form effective drug combinations for GBM.

Journal Title: PloS one

PUBMED ID: 23053494

DOI: doi.org/10.1007/s10014-012-0118-9

Titolo: Progressive adult primary glioblastoma in the medulla oblongata with an unmethylated MGMT promoter and without an IDH mutation.

Autori: Yoshikawa A., Nakada M., Watanabe T., Hayashi Y., Sabit H., Kato Y., Suzuki S., Ooi A., Sato H., Hamada J.

Data di Pubblicazione: 2012-10-12

Abstract: A 63-year-old woman presented with dizziness followed by gait disturbance and loss of appetite. Magnetic resonance image (MRI) showed that a lesion located in the medulla oblongata, appearing as hyperintense on T2-weighted image and with slight enhancement area, appeared in the ventral aspect of the mass on T1-weighted MR imaging with gadolinium. It was diagnosed as high-grade brain-stem glioma and the patient underwent chemoradiotherapy. However, she died 18 days after treatment, and autopsy was performed. The pathological diagnosis was glioblastoma (GBM) with unmethylated O-6-methylguanine-DNA methyltransferase promoter and wild isocitrate dehydrogenase 1 gene. We report an extremely short clinical course of adult GBM in medulla oblongata with genetic analysis and present a review of the literature.

Journal Title: Brain tumor pathology

PUBMED ID: 23043578

DOI: doi.org/10.1111/j.1754-9485.2012.02414.x

Titolo: The addition of temozolomide does not change the pattern of progression of glioblastoma multiforme post-radiotherapy.

Autori: Gunjur A., Bressel M., Ryan G.

Data di Pubblicazione: 2012-10-10

Abstract: The pattern of progression in our GBM patients does not appear to have been altered by the addition of temozolomide. The overwhelming majority of first PD occurred within the original radiotherapy planning target volume, as is the case in patients treated with radiotherapy alone. Major changes to radiotherapy volumes are not indicated, with alternative strategies required to improve outcomes.

Journal Title: Journal of medical imaging and radiation oncology



PUBMED ID: 23039151

DOI: doi.org/10.3171/2012.9.JNS12504

Titolo: Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article.

Autori: Bloch O., Han S.J., Cha S., Sun MZ., Aghi MK., McDermott MW., Berger MS., Parsa AT.

Data di Pubblicazione: 2012-10-9

Abstract: Extent of resection at recurrence is an important predictor of overall survival. If GTR is achieved at recurrence, overall survival is maximized regardless of initial EOR, suggesting that patients with initial STR may benefit from surgery with a GTR at recurrence.

Journal Title: Journal of neurosurgery

PUBMED ID: 23019233

DOI: doi.org/10.1093/neuonc/nos213

Titolo: Lack of efficacy of bevacizumab + irinotecan in cases of pediatric recurrent ependymoma--a Pediatric Brain Tumor Consortium study.

Autori: Gururangan S., Fangusaro J., Young Poussaint T., Onar-Thomas A., Gilbertson RJ., Vajapeyam S., Gajjar A., Goldman S., Friedman HS., Packer RJ., Boyett JM., Kun LE., McLendon R.

Data di Pubblicazione: 2012-9-29

Abstract: A phase II study of bevacizumab (BVZ) plus irinotecan (CPT-11) was conducted in cases of pediatric recurrent ependymoma (EPN) to estimate sustained objective response rate and progression-free survival (PFS). Eligible patients received 2 doses of single-agent BVZ intravenously (10 mg/kg) 2 weeks apart and then BVZ + CPT-11 every 2 weeks until progressive disease, unacceptable toxicity, or a maximum of 2 years of therapy. Correlative studies included diffusion-weighted and T1 dynamic contrast enhanced permeability imaging and tumor immunohistochemistry for vascular endothelial growth factor (VEGF)-A and -B, hypoxia inducible factor-2 $\alpha$ , VEGF receptor (R)-2, and carbonic anhydrase (CA)-9. Thirteen evaluable patients received a median of 3 courses (range, 2-12) of BVZ + CPT-11. No sustained response was observed in any patient. Median time to progression in 10 patients was 2.2 months (range, 1.9-6.3). Two patients had stable disease for 10 months and 12 months, respectively. Six-month PFS was 25.7% (SE = 11.1%). Grades I-III toxicities related to BVZ treatment included fatigue in 4 patients, systemic hypertension in 2, epistaxis in 1, headache in 1, and avascular necrosis of bone in 1. Although there was a decrease in the mean diffusion ratio following 2 doses of BVZ, it did not correlate with PFS. BVZ + CPT-11 was well tolerated but had minimal efficacy in cases of recurrent EPN.

Journal Title: Neuro-oncology

PUBMED ID: 23017192

DOI: doi.org/10.1016/j.ejrad.2012.09.001

Titolo: Automatic multi-modal MR tissue classification for the assessment of response to bevacizumab in patients with glioblastoma.

Autori: Liberman G., Louzoun Y., Aizenstein O., Blumenthal DT., Bokstein F., Palmon M., Corn BW., Ben Bashat D.

Data di Pubblicazione: 2012-9-29

Abstract: This study emphasizes the important role of automatic tools based on a multi-modal view of the tissue in monitoring therapy response in patients with high grade gliomas specifically under anti-angiogenic therapy.

Journal Title: European journal of radiology

PUBMED ID: 22976140

DOI: doi.org/10.2176/nmc.52.570

Titolo: Effectiveness of maximal safe resection for glioblastoma including elderly and low Karnofsky performance status patients: retrospective review at a single institute.

Autori: Uzuka T., Aoki H., Natsumeda M., Takahashi H., Fujii Y.

Data di Pubblicazione: 2012-9-15

Abstract: Elderly and low Karnofsky performance status (KPS) patients have been excluded from most prospective trials. This retrospective study investigated glioblastoma treatment outcomes, including those of elderly and low KPS patients, and analyzed the prognostic factors using the medical records of 107 consecutive patients, 59 men and 48 women aged from 21 to 85 years (median 65 years), with newly diagnosed glioblastoma treated at our institute. There were 71 high-risk patients with age >70 years and/or KPS <70%. Based on the extent of resection, the patients were classified into 3 groups: more than subtotal resection (subtotal, n = 44), partial resection (partial, n = 29), and biopsy only (biopsy, n = 34). Median overall survival (OS) of all 107 patients was 13.5 months. Median OS was 13.2 months in the high-risk group. Median OSs were 15.8, 12.8, and 12.1 months in the subtotal, partial, and biopsy groups, respectively. Multivariate analysis of 73 patients in the subtotal and partial groups found age ≤65 years (p = 0.047), 60 Gy irradiation (p = 0.009), O(6)-methylguanine-deoxyribonucleic acid methyltransferase-negative (p = 0.027), and more than subtotal removal (p = 0.003) were significant prognostic factors. The median postoperative KPS score tended to be better than the preoperative score, even in the high-risk group. We recommend maximal safe resection for glioblastoma patients, even those with advanced age and/or with low KPS scores.

Journal Title: Neurologia medico-chirurgica

PUBMED ID: 22957524

DOI: doi.org/10.3171/2012.7.JNS111260

Titolo: Long-term outcomes for low-grade intracranial ganglioglioma: 30-year experience from the Mayo Clinic.

Autori: Compton JJ., Laack NN., Eckel LJ., Schomas DA., Giannini C., Meyer FB.

Data di Pubblicazione: 2012-9-11

Abstract: This single-institution retrospective series of patients with gangliogliomas is unique given its large cohort size with a long follow-up duration, and confirms the excellent long-term survival rate in this group. The study also shows the importance of resection extent on likelihood of recurrence. Patients with gangliogliomas who undergo STR or biopsy alone have poor PFS. Radiation therapy may delay time to progression in patients with unresectable disease.

Journal Title: Journal of neurosurgery

PUBMED ID: 22949057

DOI: doi.org/10.1002/pbc.24274

Titolo: Phase II study of pre-irradiation chemotherapy for childhood intracranial ependymoma. Children's Cancer Group protocol 9942: a report from the Children's Oncology Group.

Autori: Garvin JH., Selch MT., Holmes E., Berger MS., Finlay JL., Flannery A., Goldwein JW., Packer RJ., Rorke-Adams LB., Shiminski-Maher T., Sposto R., Stanley P., Tannous R., Pollack IF., Pollack IF.

Data di Pubblicazione: 2012-9-6

Abstract: Children with near total resection of ependymoma may benefit from pre-irradiation chemotherapy. Patients with subtotal resection have inferior outcome despite responses to chemotherapy, and should be considered for second-look surgery prior to irradiation. *Pediatr Blood Cancer* 2012; 59: 1183-1189. © 2012 Wiley Periodicals, Inc.

Journal Title: Pediatric blood & cancer

PUBMED ID: 22946346

DOI: Mancante

Titolo: Phase I/II study of oral erlotinib for treatment of relapsed/refractory glioblastoma multiforme and anaplastic astrocytoma.

Autori: Kesavabhotla K., Schlaff CD., Shin B., Mubita L., Kaplan R., Tsiouris AJ., Pannullo SC., Christos P., Lavi E., Scheff R., Boockvar JA.

Data di Pubblicazione: 2012-9-6

Abstract: We evaluated the safety and survival benefits of orally administered erlotinib monotherapy for patients with relapsed/refractory glioblastoma multiforme (GBM) or anaplastic astrocytoma (AA). A dose escalation schedule was administered with a starting dose of 150 mg/day for the first cycle (28 days), followed by 100 mg twice daily for 14 days, and 150 mg twice daily for another 14 days. Assuming no dose limiting toxicities were observed, dosage was maintained at 150 mg BID for 10 more cycles. Disease and tumor responses were assessed after every other cycle; toxicity assessments were conducted for a minimum of 10 weeks. Patients discontinued use of enzyme-inducing anticonvulsants (EIAED) and started non-EIAEDs. Patients with previous erlotinib exposure were ineligible. Eleven patients were enrolled: 8 (73%) GBM; 3 (27%) AA. Adverse events limited study accrual, originally intended to accrue 43 patients. Nine patients (90%) experienced rash within the first 2 cycles: 7 (64%) within cycle 1; 6 (60%) reported diarrhea within the first 2 cycles. Median progress-free survival (PFS) and overall survival (OS) was 1.9 months and 6.9 months. All patients showed disease progression while on the drug. Despite the sample size, the toxicity of erlotinib supersedes any marginal benefit it as a monotherapy for relapsed/refractory GBM/AA.

Journal Title: Journal of experimental therapeutics & oncology

PUBMED ID: 22932984

DOI: doi.org/10.1007/s11060-012-0964-7

Titolo: Phase I trial of verubulin (MPC-6827) plus carboplatin in patients with relapsed glioblastoma multiforme.

Autori: Grossmann KF., Colman H., Akerley WA., Glantz M., Matsuoka Y., Beelen AP., Yu M., De Groot JF., Aiken RD., Olson JJ., Olsen JJ., Evans BA., Jensen RL.

Data di Pubblicazione: 2012-8-31

Abstract: Verubulin (MPC-6827) is a microtubule-destabilizing agent that achieves high concentrations in the brain. Verubulin disrupts newly formed blood vessels in xenografts. We determined the safety and tolerability of verubulin administered in combination with carboplatin in patients with relapsed glioblastoma multiforme (GBM). Three pre-selected doses of verubulin were tested: 2.1, 2.7, and 3.3 mg/m<sup>2</sup> in a standard "3+3" design. Verubulin was given every second week of a 6-week cycle in the 2.1 mg/m<sup>2</sup> cohort or weekly for 3 weeks of a 4-week cycle in subsequent cohorts. Carboplatin was administered intravenously at an area under the curve (AUC) dosage 4 every 2 weeks for the 2.1 mg/m<sup>2</sup> cohort or on day 1 of each 4-week cycle in subsequent cohorts. Nineteen patients with GBM in first or second relapse were enrolled. Four patients (21 %) experienced a grade 3 or greater verubulin- or carboplatin-related adverse event, including hypesthesia, cerebral ischemia, anemia, and thrombocytopenia. The mean plasma half life of verubulin was 3.2 h (SD = 0.82). Two patients achieved at least a partial response by Macdonald criteria. One of these patients remains progression free and off treatment more than 24 months beyond his initiation of verubulin. Five patients had stable disease. Median progression-free survival (PFS) across all patients was 8 weeks, and the 6-month PFS rate was 21 %. The combination of verubulin at the previously determined single-agent maximum tolerated dose of 3.3 mg/m<sup>2</sup> with carboplatin in patients with recurrent/refractory GBM is safe and well tolerated.

ated. In this patient population with a highly vascularized tumor, no cerebral hemorrhage was observed.

Journal Title: Journal of neuro-oncology

PUBMED ID: 22913972

DOI: doi.org/10.1097/CCO.0b013e328357f503

Titolo: Chemotherapy in low-grade gliomas.

Autori: Viacoz A., Lekoubou A., Ducray F.

Data di Pubblicazione: 2012-8-24

Abstract: It has now been widely accepted that chemotherapy is an interesting treatment option in LGGs. However, several questions remain unanswered regarding its optimal use. Ongoing phase III studies will allow a better delineation of the role of chemotherapy in LGGs and will also help to better determine the potential predictive value of a 1p/19q codeletion, a MGMT promoter methylation and an IDH1 mutation.

Journal Title: Current opinion in oncology

PUBMED ID: 22877848

DOI: doi.org/10.1016/S1470-2045(12)70265-6

Titolo: Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial.

Autori: Malmström A., Grønberg BH., Marosi C., Stupp R., Frappaz D., Schultz H., Abacioglu U., Tavelin B., Lhermitte B., Hegi ME., Rosell J., Henriksson R., Henriksson R.

Data di Pubblicazione: 2012-8-11

Abstract: Merck, Lion's Cancer Research Foundation, University of Umeå, and the Swedish Cancer Society.

Journal Title: The Lancet. Oncology

PUBMED ID: 22825915

DOI: doi.org/10.3892/ijo.2012.1564

Titolo: IDH1/2 mutation is a prognostic marker for survival and predicts response to chemotherapy for grade II gliomas concomitantly treated with radiation therapy.

Autori: Okita Y., Narita Y., Miyakita Y., Ohno M., Matsushita Y., Fukushima S., Sumi M., Ichimura K., Kayama T., Shibui S.

Data di Pubblicazione: 2012-7-25

Abstract: Reliable prognostic biomarkers of grade II gliomas remain unclear. This study aimed to examine the role of mutations of isocitrate dehydrogenase (IDH1/2), 1p/19q co-deletion, and clinicopathological factors in patients with grade II glioma who were primarily treated with radiotherapy or chemoradiotherapy after surgery. Seventy-two consecutive patients, including 49 cases of diffuse astrocytomas (DA), 4 oligodendrogliomas (OL) and 19 oligoastrocytomas (OA), who underwent treatment from 1991 to 2010 at a single institution were examined. The overall survival (OS) of the DA patients (8.3 years) was significantly shorter than that of the OL and OA patients (11.7 years). IDH1/2 mutations were found in 46.9% of the DA patients and 82.6% of the OL and OA patients. The progression-free survival (PFS) and OS of the patients with IDH1/2 mutations (8.4 and 16.3 years) were significantly longer than those of the patients without IDH1/2 mutations (3.3 and 4.5 years). Among the patients with IDH1/2 mutations, those who were initially treated with chemoradiotherapy including nimustine hydrochloride (ACNU), had significantly longer PFS than those treated with radiotherapy alone, whereas no significant difference in PFS was observed between the chemoradiotherapy and radiotherapy groups in the patients without IDH1/2 mutations. Oligodendroglioma tumors, age <40 years, initial Karnofsky performance status (KPS) ≥80, and IDH1/2 muta

tions were favorable prognostic factors regarding PFS and OS. IDH1/2 mutation was a predictive factor of response to chemoradiotherapy in grade II gliomas. Patients with IDH1/2 mutations may benefit more from chemoradiotherapy than those without IDH1/2 mutations.

Journal Title: International journal of oncology

PUBMED ID: 22809568

DOI: doi.org/10.1016/j.canlet.2012.07.012

Titolo: Increasing the efficacy of tumor cell vaccines by enhancing cross priming.

Autori: Andersen BM., Ohlfest JR.

Data di Pubblicazione: 2012-7-20

Abstract: Cancer immunotherapy has been attempted for more than a century, and investment has intensified in the last 20 years. The complexity of the immune system is exemplified by the myriad of immunotherapeutic approaches under investigation. While anti-tumor immunity has been achieved experimentally with multiple effector cells and molecules, particular promise is shown for harnessing the CD8 T cell response. Tumor cell-based vaccines have been employed in hundreds of clinical trials to date and offer several advantages over subunit and peptide vaccines. However, tumor cell-based vaccines, often aimed at cross priming tumor-reactive CD8 T cells, have shown modest success in clinical trials. Here we review the mechanisms of cross priming and discuss strategies to increase the efficacy of tumor cell-based vaccines. A synthesis of recent findings on tissue culture conditions, cell death, and dendritic cell activation reveals promising new avenues for clinical investigation.

Journal Title: Cancer letters

PUBMED ID: 22798016

DOI: doi.org/10.1007/s11864-012-0205-5

Titolo: Current treatment options for pediatric and adult patients with ependymoma.

Autori: Wright KD., Gajjar A.

Data di Pubblicazione: 2012-7-17

Abstract: Survival rates for patients with ependymoma, a glial tumor arising from the ependymal cells lining the ventricles of the brain and spinal cord canal, have changed little during the past decade. Contemporary "standard" therapy for children and adults with ependymoma consists of maximal surgical resection followed by focal irradiation except in cases of disseminated disease. Despite refinements in radiotherapy techniques and improvements in survival for patients with gross totally resected, nonanaplastic disease, many therapeutic challenges remain, especially for patients with unresectable, macroscopic, metastatic, or anaplastic disease. Moreover, radiotherapy to the developing central nervous system, especially in patients younger than age 5 years, can have potential long-term neurocognitive and neuroendocrine sequelae. Chemotherapy has not played a role in most treatment regimens for ependymoma to date, but due to the ongoing therapeutic challenges for a subset of patients, this modality is being reinvestigated in a few ongoing studies. Early recognition of patients who will not respond to primary therapy is imperative to modify treatment regimens, such as intensification with the addition of adjuvant chemotherapy, the use of novel experimental therapies, or their combination. Refinements in patient stratification schemes that are based on a combination of clinical variables and molecular profiles also require improved knowledge of tumor biology. Several molecular alterations have been identified already, some of which may be of prognostic significance. Furthermore, disruption of molecular alterations in signaling pathways involved in the development and maintenance of ependymoma by using novel molecularly targeted therapies may improve outcomes and reduce toxicity for patients with ependymoma.

Journal Title: Current treatment options in oncology

PUBMED ID: 22745043

DOI: doi.org/10.1002/pbc.24244

Titolo: Phase 2 trial of pemetrexed in children and adolescents with refractory solid tumors: a Children's Oncology Group study.

Autori: Warwick AB., Malempati S., Krailo M., Melemed A., Gorlick R., Ames M M., Safgren SL., Adamson PC., Blaney SM.

Data di Pubblicazione: 2012-6-30

Abstract: Pemetrexed, administered as an intravenous infusion every 21 days, was tolerable in children and adolescents with refractory solid tumors, including CNS tumors, but did not show evidence of objective anti-tumor activity in the childhood tumors studied.

Journal Title: Pediatric blood & cancer

PUBMED ID: 22744756

DOI: doi.org/10.1007/s11060-012-0913-5

Titolo: Procarbazine, carmustine, and vincristine (PBV) for chemotherapy pre-treated patients with recurrent glioblastoma: a single-institution analysis

Autori: Kuhnhen J., Kowalski T., Steenken S., Ostermann K., Schlegel U.

Data di Pubblicazione: 2012-6-30

Abstract: In newly diagnosed glioblastoma multiforme, surgery, combined radio and chemotherapy, and adjuvant chemotherapy with temozolomide is the standard of care. Therapy for recurrent glioblastoma is less well established and comprises re-operation, re-irradiation, chemotherapy, targeted therapy, inhibition of neoangiogenesis, and others. In this observational study we recorded the efficacy and toxicity of a combination of procarbazine, carmustine, and vincristine (PBV) for 69 patients with recurrent and/or progressive glioblastoma after surgery, concomitant radio and/or chemotherapy, and adjuvant first-line temozolomide therapy. Of 41 patients evaluable for response by MRI, partial response was observed for one, minor response for three, stable disease for at least 6 weeks for ten, and immediate progression for 27. Median PFS was 15 weeks, and PFS-6 was 21 % for 57 patients who could be followed; 12 other patients were lost to follow-up after application of the first PBV cycle. Grade III or IV leucopenia and/or grade III or IV thrombocytopenia were seen in 26 % and 26 % of cycles, respectively. Haematological complications led to interruption of treatment for four (7 %) patients. Non-haematological toxicity was moderate. Salvage PBV therapy in recurrent and/or progressive glioblastoma, pre-treated with temozolomide-based chemotherapy as first-line treatment, is of limited efficacy with a small number of long-term survivors, but is hampered by relevant myelotoxicity.

Journal Title: Journal of neuro-oncology

PUBMED ID: 22740218

DOI: Mancante

Titolo: Long term experience in high grade glial tumors with temozolomide.

Autori: Demirci U., Buyukberber S., Coskun U., Akmansu M., Yaman E., Baykara M., Yamac D., Uner A., Benekli M.

Data di Pubblicazione: 2012-6-29

Abstract: Temozolomide is an effective agent in HGGs with favorable outcome and low toxicity profile even in advanced age.

Journal Title: Journal of B.U.ON. : official journal of the Balkan Union of Oncology

PUBMED ID: 22711608

DOI: doi.org/10.1093/neuonc/nos125

Titolo: Clinical and molecular characteristics of congenital glioblastoma.

Autori: Macy ME., Birks DK., Barton VN., Chan MH., Donson AM., Kleinschmidt-Demasters BK., Bemis LT., Handler MH., Foreman NK.

Data di Pubblicazione: 2012-6-20

Abstract: Congenital glioblastoma (cGBM) is an uncommon tumor of infancy with a reported variable but often poor cure rate, even with intensive therapy. Five patients with cGBMs, arising de novo and not in familial tumor predisposition kindreds, were studied for histological and biological features, using Affymetrix microarray. Tumors were large, often associated with hemorrhage, extended into the thalamus, and often bulged into the ventricles. One patient died acutely from bleeding at the time of operation. The 4 surviving patients underwent surgery (1 gross total resection, 3 subtotal resections or biopsies) and moderate intensity chemotherapy without radiation, and remain progression-free at a median time of 36 months (range, 30-110 months). Affymetrix microarrays measured gene expression on the 3 cGBMs from which frozen tissue was available. Unsupervised hierarchical clustering of cGBMs versus 168 other central nervous system tumors demonstrated that cGBMs clustered most closely with other high-grade gliomas. Gene expression profiles of cGBMs were compared with non-congenital pediatric and adult GBMs. cGBMs demonstrated marked similarity to both pediatric and adult GBMs, with only 31 differentially expressed genes identified (false discovery rate, <0.05). Unique molecular features of cGBMs included over-expression of multiple genes involved in glucose metabolism and tissue hypoxia. cGBMs show histological and biological overlap with pediatric and adult GBMs but appear to have a more favorable outcome, with good response to moderate intensity chemotherapy with only subtotal resection or biopsy. Further study may determine whether identified gene expression differences contribute to the improved survival seen in these tumors.

Journal Title: Neuro-oncology

PUBMED ID: 22688802

DOI: doi.org/10.1007/s11060-012-0906-4

Titolo: Radiotherapy and concomitant temozolomide may improve survival of elderly patients with glioblastoma.

Autori: Barker CA., Chang M., Chou JF., Zhang Z., Beal K., Gutin PH., Iwamoto FM.

Data di Pubblicazione: 2012-6-13

Abstract: Survival of elderly patients with glioblastoma (GBM) is poor, but improves with tumor resection and radiotherapy (RT). Concurrent temozolomide (TMZ) chemotherapy during RT improves the survival of younger patients with GBM, but the benefit in elderly patients is unclear. Medical records of patients  $\geq 65$  years old with primary GBM, histologically confirmed at Memorial Sloan-Kettering Cancer Center and treated with RT, were reviewed. Survival was associated with patient (age, performance status), tumor (single or multiple), and treatment (extent of surgery, RT field, technique, fractionation and use of concurrent TMZ) characteristics in a multivariable Cox regression model. Grade  $\geq 3$  hematologic toxicity rates were compared to reported rates in younger patients. Median age of the 291 patients studied was 71 years. Longer survival was associated with younger age, tumor resection, and concomitant TMZ and RT ( $p < 0.01$ ). Concurrent TMZ and RT improved median survival of patients with favorable prognostic factors from 12 to 21 months and from 10 to 13 months in patients 65-70 and  $\geq 71$  years old, respectively. Concomitant TMZ and RT increased the 2 year OS rate from 14 to 41 % and from 5 to 24 % in patients 65-70 and  $\geq 71$  years old, respectively. Grade 3-4 thrombocytopenia was significantly more frequent in the present cohort. Survival of elderly patients with GBM may be prolonged with the use of concomitant TMZ during RT. An ongoing randomized study will determine the benefit of this approach in a prospective fashion.

Journal Title: Journal of neuro-oncology

PUBMED ID: 22688083

DOI: doi.org/10.1159/000339152

Titolo: Patupilone (epothilone B) for recurrent glioblastoma: clinical outcome and translational analysis of a single-institution phase I/II trial.

Autori: Oehler C., Frei K., Rushing EJ., McSheehy PM., Weber D., Allegrini P R., Weniger D., Lütolf UM., Knuth A., Yonekawa Y., Barath K., Broggini-Tenzer A., Pruschy M., Hofer S.

Data di Pubblicazione: 2012-6-13

Abstract: In recurrent GBM, patupilone can be given safely pre- and postoperatively. The drug accumulates in the tumor tissue. The treatment results in long-term PFS in some patients. Patupilone represents a valuable novel compound which deserves further evaluation in combination with radiation therapy in patients with GBM.

Journal Title: Oncology

PUBMED ID: 22679179

DOI: doi.org/10.1158/1078-0432.CCR-12-0568

Titolo: Vismodegib.

Autori: Rudin CM.

Data di Pubblicazione: 2012-6-9

Abstract: Vismodegib (GDC-0449), an orally bioavailable small-molecule inhibitor of Hedgehog signaling, was recently approved by the U.S. Food and Drug Administration for the treatment of basal cell carcinoma that is either metastatic or locally advanced in patients who are not candidates for surgical resection or radiation. Given the absence of previously defined effective drug therapy for this disease, approval was granted primarily on the basis of outcome of a nonrandomized parallel cohort phase II study of 99 patients with advanced basal cell carcinoma, with a primary endpoint of objective response rate. Response rates of 30.3% and 42.9% were observed in metastatic and locally advanced cohorts in this study, respectively, associated with median progression-free survival in both cohorts of 9.5 months. Ongoing clinical investigations include evaluation of the potential efficacy of vismodegib in a variety of diseases and in combination with other agents. The mechanism of action, preclinical and clinical data, and potential utility in other disease contexts are reviewed here.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 22665539

DOI: doi.org/10.1200/JCO.2011.40.2792

Titolo: Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study.

Autori: Jakacki RI., Burger PC., Zhou T., Holmes EJ., Kocak M., Onar A., Gollwein J., Mehta M., Packer RJ., Tarbell N., Fitz C., Vezina G., Hilden J., Pollack IF.

Data di Pubblicazione: 2012-6-6

Abstract: The use of carboplatin as a radiosensitizer is a promising strategy for patients with M+ MB. Early progression should be confirmed by biopsy.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 22665535

DOI: doi.org/10.1200/JCO.2011.36.6054



Titolo: Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group.  
Autori: Ater JL., Zhou T., Holmes E., Mazewski CM., Booth TN., Freyer DR., Lazarus KH., Packer RJ., Prados M., Sposto R., Vezina G., Wisoff JH., Pollack IF.

Data di Pubblicazione: 2012-6-6

Abstract: PURPOSE Surgery is curative therapy for pediatric low-grade gliomas (LGGs) in areas of the brain amenable to complete resection. However, LGGs located in areas where complete resection is not possible can threaten both function and life. The purpose of this study was to compare two chemotherapy regimens for LGGs in children younger than age 10 years for whom radiotherapy was felt by the practitioner to pose a high risk of neurodevelopmental injury. PATIENTS AND METHODS Previously untreated children younger than age 10 years with progressive or residual LGGs were eligible. Children were randomly assigned to receive carboplatin and vincristine (CV) or thioguanine, procarbazine, lomustine, and vincristine (TPCV). Children with neurofibromatosis are reported separately. Results Of 274 randomly assigned patients who met eligibility requirements, 137 received CV and 137 received TPCV. The 5-year event-free survival (EFS) and overall survival (OS) rates for all eligible patients were  $45\% \pm 3.2\%$  and  $86\% \pm 2.2\%$ , respectively. The 5-year EFS rates were  $39\% \pm 4\%$  for CV and  $52\% \pm 5\%$  for TPCV (stratified log-rank test  $P = .10$ ; cure model analysis  $P = .007$ ). On multivariate analysis, factors independently predictive of worse EFS and OS were younger age and tumor size greater than 3 cm(2). Tumor location in the thalamus was also associated with poor OS. CONCLUSION The difference in EFS between the regimens did not reach significance on the basis of the stratified log-rank test. The 5-year EFS was higher for TPCV on the basis of the cure model analysis. Differences in toxicity may influence physician choice of regimens.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 22661588

DOI: doi.org/10.1093/neuonc/nos123

Titolo: Antioxidant enzyme polymorphisms and neuropsychological outcomes in medulloblastoma survivors: a report from the Childhood Cancer Survivor Study

Autori: Brackett J., Krull KR., Scheurer ME., Liu W., Srivastava DK., Stoval M., Merchant TE., Packer RJ., Robison LL., Okcu MF.

Data di Pubblicazione: 2012-6-5

Abstract: Psychological or neurocognitive impairment is often seen in medulloblastoma survivors after craniospinal radiation; however, significant variability in outcomes exists. This study investigated the role of antioxidant enzyme polymorphisms in moderating this outcome and hypothesized that patients who had polymorphisms associated with lower antioxidant enzyme function would have a higher occurrence of impairment. From the Childhood Cancer Survivor Study (CCSS) cohort, 109 medulloblastoma survivors and 143 siblings were identified who completed the CCSS Neurocognitive Questionnaire (NCQ) and the Brief Symptom Inventory-18 (BSI-18) and who provided buccal DNA samples. Real-time polymerase chain reaction (PCR) allelic discrimination was used for SOD2 (rs4880), GPX1 (rs1050450), and GSTP1 (rs1695 and rs1138272) genotyping and PCR for GSTM1 and GSTT1 gene deletions. Outcomes on NCQ and BSI-18 subscale scores were examined in association with genotypes and clinical factors, including age at diagnosis, sex, and radiation dose, using univariate and multivariate analysis of variance. Patients <7 years of age at diagnosis displayed more problems with task efficiency ( $P < .001$ ) and fewer problems with somatic complaints ( $P = .004$ ) than did patients  $\geq 7$  years of age. Female patients reported more organization problems than did male patients ( $P = .02$ ). Patients with homozygous GSTM1 gene deletion reported higher anxiety (mean null genotype =  $47.3 \pm 9.2$ , non-null =  $43.9 \pm 7.8$ ;  $P = .04$ ), more depression (n

ull =  $51.0 \pm 9.8$ , non-null =  $47.0 \pm 9.4$ ;  $P = .03$ ), and more global distress (null =  $50.2 \pm 9.7$ , non-null =  $45.2 \pm 9.9$ ;  $P = .01$ ). All associations for the GSTM1 polymorphism remained statistically significant in a multivariate model controlling for age, sex, and radiation dose. Homozygous GSTM1 gene deletion was consistently associated with greater psychological distress in medulloblastoma survivors across multiple domains, suggesting that this genotype may predispose patients for increased emotional late effects.

Journal Title: Neuro-oncology

PUBMED ID: 22650980

DOI: doi.org/10.1517/17460441.2011.584530

Titolo: Advances in malignant glioma drug discovery.

Autori: Reardon DA., Perry JR., Brandes AA., Jalali R., Wick W.

Data di Pubblicazione: 2012-6-2

Abstract: Several factors limit the efficacy of therapeutics targeting GBM. However, significant advances from basic science laboratories have recently generated important insights into the pathophysiology and molecular genetic abnormalities of these tumors. Efforts to translate these findings into innovative treatment strategies offer substantial promise to overcome therapeutic hurdles and treat individual patients more effectively. Improved understanding of malignant glioma biology and factors associated with treatment response will probably lead to improved therapeutic options and a better patient outcome.

Journal Title: Expert opinion on drug discovery

PUBMED ID: 28519041

DOI: doi.org/10.1118/1.4735032

Titolo: SU-E-J-191: A Multivariate Framework for N-Tissue Classification in Treatment Assessment of Glioblastomas.

Autori: Schreibmann E., Crocker I., Shu H., Curran W., Fox T.

Data di Pubblicazione: 2017-5-19

Abstract: Usage of advanced classification techniques allows automated labeling of voxels into normal, pseudoprogression or tumoral tissue types. The technique allows for early detection of pseudo progression to spare patients from unnecessary surgery or toxic chemotherapy.

Journal Title: Medical physics

PUBMED ID: 22629849

DOI: Mancante

Titolo: [Stereotactic radiotherapy and radiosurgery in treatment of patients with deep-seated pilocytic astrocytomas].

Autori: Trunin IuIu., Golanov AV., Konovalov AN., Shishkina LV., Gorlachev G E., Gorelyshev SK., Pronin IN., Khukhlaeva EA., Serova NK., Korshunov AG., Melikyan AG., Ryzhova MV., Kadyrov ShU., Sorokin VS., Mazerkina NA., Mariashev SA., Il'ialov SR., Kostiuchenko VV.

Data di Pubblicazione: 2012-5-29

Abstract: Pilocytic astrocytoma (PA) is a low-grade glial tumor (WHO grade I) with predominant occurrence in pediatric patients. According to many authors, stereotactic radiosurgery (SRS) and radiotherapy (SRT) promote long-term remission or retardation of tumor progression in patients with inoperable lesions after incomplete resection or recurrence. Therefore it is essential to determine the role of SRS and SRT in complex management of patients with deep-seated PA. Since April 2005 till May 2010 101 patient with intracranial PA was treated in department for radiation therapy of Burdenko Neurosurgical Institute. The series consisted of 70 pediatric patients (below 17 years inclusively) and 31 adults, of them--51 male and 50 female patients. Mean age was 15.1 years (9.8 years in children and 28.7 in adults). In 90 patients (89

.2%) tumors were previously histologically verified (tumor resection in 83 cases and biopsy in 7). In 11 (10.8%) patients diagnosis of PA was based on clinical and neurovisualization data. In most cases SRT (66 (66.3%) patients) was preformed, the rest 35 (34.7%) patients were treated by SRS. Median follow-up from the onset of disease reached 52 months (2-228 months). Cataamnesti c data were available in 88 (87%) patients. By the end of catamnesitic follow-up (December 2010) 87 (98.8%) patients treated by SRS and SRT were alive. Median follow-up from the start of radiation treatment was 22.7 months (6-60 months). Progression of tumor was observed in 20 patients (22.7%), in 18 of them due to cyst growth. 18 patients were reoperated. In 12 operated patients histological examination and its comparative analysis were performed. We found that alterations in the tumor tissue, accompanied by regression of solid component and progression of cystic portion, represent reactive-degenerative changes in the tumor as a consequence of radiation-induced pathomorphism. SRS and STR are effective techniques for treatment of patients with primary and recurrent PA despite regardless of localization of the tumor. There procedures should be performed shortly after non-radical resection. Control of tumor growth by the present time (median follow-up is 22.7 months) reaches 98 %. "Progression" of the tumor due to enlargement of cystic portion shortly after SRT and SRS represents reactive-degenerative alterations in the tumor tissue and should not be evaluated as true recurrence; without neurological deterioration these cases do not require special treatment.

Journal Title: Zhurnal voprosy neirokhirurgii imeni N. N. Burdenko

PUBMED ID: 22594978

DOI: doi.org/10.1016/j.pdpdt.2012.01.001

Titolo: Preliminary clinical report on safety and efficacy of photodynamic therapy using talaporfin sodium for malignant gliomas.

Autori: Akimoto J., Haraoka J., Aizawa K.

Data di Pubblicazione: 2012-5-19

Abstract: We examined the safety and efficacy of PDT using talaporfin sodium as an additional intraoperative treatment for malignant glioma. PDT in addition to surgical resection achieved better therapeutic results than conventional protocols, especially in patients with newly diagnosed malignant gliomas. However, the current methodology has some limitations with respect to patients with recurrent tumors. Larger-scale studies are required to confirm the clinical feasibility of PDT plus surgery.

Journal Title: Photodiagnosis and photodynamic therapy

PUBMED ID: 22580799

DOI: doi.org/10.1007/s11060-012-0889-1

Titolo: Stereotactic iodine-125 brachytherapy for treatment of inoperable focal brainstem gliomas of WHO grades I and II: feasibility and long-term outcome.

Autori: Ruge MI., Kickingeder P., Simon T., Treuer H., Sturm V.

Data di Pubblicazione: 2012-5-15

Abstract: Microsurgical resection is the most frequently suggested treatment option for accessible focal brainstem gliomas (F-BSG) of World Health Organization (WHO) grades I and II. Because of their location in the highly eloquent brain, however, resection is associated with permanent postoperative morbidity, ranging from 12 to 33 %. Only a few reports have suggested stereotactic brachytherapy (SBT) with implantation of iodine-125 seeds as a local treatment alternative. Between 1993 and 2010, 47 patients were treated with SBT (iodine-125 seeds; cumulative surface dose 50-65 Gy) for inoperable F-BSG, WHO grades I and II, in one of the largest reported patient series. We evaluated procedure-related complications, clinical outcome, and progression-free and overall survival (PFS, OS). Median follow-up was 81.6 months. Procedure-related mortality was zero. Within 30 days of seed implantation six patients

(12.8 %) had transient neurological deficits. Two patients (4.3 %) deteriorated permanently. Space-occupying cysts occurred in six patients (12.8 %) after a median of 28.5 months, and required surgical intervention. Nine patients (19.1 %) presented with tumor relapse after a median of 56.6 months (range 7.9-118.0 months). For the remaining 38 patients complete response was observed for 23.4 %, partial response for 29.8 %, and stable disease for 27.7 %. Actuarial PFS was  $97.7 \pm 2.2$ ,  $92.8 \pm 4.0$ ,  $81.2 \pm 6.5$ , and  $62.0 \pm 10.4$  % after 1, 2, 5, and 10 years, respectively. Corresponding OS was  $100 \pm 0.0$  % (1 and 2 years),  $97.4 \pm 2.6$  % (5 years), and  $87.6 \pm 7.0$  % (10 years). SBT is a comparatively safe, minimally invasive, and highly effective local treatment option for patients with inoperable F-BSG WHO grades I and II; it merits further evaluation in prospective randomized trials.

Journal Title: Journal of neuro-oncology

PUBMED ID: 22576886

DOI: doi.org/10.3174/ajnr.A3091

Titolo: Metabolic response of glioblastoma to superselective intra-arterial cerebral infusion of bevacizumab: a proton MR spectroscopic imaging study.

Autori: Jeon JY., Kovanlikaya I., Boockvar JA., Mao X., Shin B., K Burkhardt J., Kesavabhotla K., Christos P., Riina H., Shungu DC., Tsiouris AJ.

Data di Pubblicazione: 2012-5-12

Abstract: The results of this (1)H-MRS analysis suggest that GB treatment with SIACI of bevacizumab may be associated with a direct antiproliferative effect, as demonstrated by significant reductions of tCho/NAA after the intervention.

Journal Title: AJNR. American journal of neuroradiology

PUBMED ID: 22555992

DOI: doi.org/10.1007/s11060-012-0887-3

Titolo: Can irradiation of potential cancer stem-cell niche in the subventricular zone influence survival in patients with newly diagnosed glioblastoma?

Autori: Gupta T., Nair V., Paul SN., Kannan S., Moiyadi A., Epari S., Jalali R.

Data di Pubblicazione: 2012-5-5

Abstract: Glioblastoma progenitor or stem cells residing in the stem-cell niche in the subventricular zones (SVZ) can initiate or promote tumorigenesis. They can also migrate throughout the brain, resulting in disease progression. Irradiation of potential cancer stem-cell niche in the SVZ may influence survival. To analyze radiotherapy dose-volume parameters to the SVZ that correlate with survival in adequately treated patients with newly diagnosed glioblastoma, 40 adults with histopathologically proven supratentorial glioblastoma with available baseline imaging treated with postoperative conventionally fractionated focal conformal radiotherapy plus chemotherapy, available radiotherapy planning dataset, and documented event of progression or death or minimum 6-month follow-up were included in this retrospective study. Dose-volume parameters to the SVZ were extracted from treatment planning system and analyzed in relation to survival outcomes. Mean ipsilateral and contralateral SVZ volumes were 5.6 and 6.4 cc, respectively. With median follow-up of 15 months (interquartile range 12-18 months), median [95 % confidence interval (CI)] progression-free survival (PFS) and overall survival (OAS) was 11 months (95 % CI 8.9-13.0 months) and 17 months (95 % CI 11.6-22.4 months), respectively. Older age (>50 years), poor recursive partitioning analysis (RPA) class, and higher than median of mean contralateral SVZ dose were associated with significantly worse PFS and OAS. Multivariate analysis identified RPA class, Karnofsky performance status, and mean ipsilateral SVZ dose as independent predictors of survival. Increasing mean dose to the ipsilateral SVZ was associated with significantly improved OAS. Irradiation of potential cancer

stem-cell niche influences survival outcomes in patients with newly diagnosed glioblastoma.

Journal Title: Journal of neuro-oncology

PUBMED ID: 22547006

DOI: doi.org/10.1097/COC.0b013e3182467efa

Titolo: Optic glioma in children: a retrospective analysis of 101 cases.

Autori: Varan A., Batu A., Cila A., Soylemezoğlu F., Balcı S., Akalan N., Zorlu F., Akyüz C., Kutluk T., Büyükpamukçu M.

Data di Pubblicazione: 2012-5-2

Abstract: Patients with NF-1 and those older than 10 years have a better prognosis, whereas patients younger than 3 years and those with hypothalamic-chiasmatic optic glioma have a worse outcome. Further studies are needed to find appropriate treatment strategies.

Journal Title: American journal of clinical oncology

PUBMED ID: 22538078

DOI: doi.org/10.3174/ajnr.A3053

Titolo: Persistent diffusion-restricted lesions in bevacizumab-treated malignant gliomas are associated with improved survival compared with matched controls.

Autori: Mong S., Ellingson BM., Nghiemphu PL., Kim HJ., Mirsadraei L., Lai A., Yong W., Zaw TM., Cloughesy TF., Pope WB.

Data di Pubblicazione: 2012-4-28

Abstract: Restricted-diffusion lesions in malignant gliomas treated with bevacizumab are generally stable with time and are associated with improved outcomes. These results combined with physiologic imaging and histopathologic data suggest that these lesions are not consistent with aggressive tumor.

Journal Title: AJNR. American journal of neuroradiology

PUBMED ID: 22527250

DOI: doi.org/10.1007/s00262-012-1261-1

Titolo: Integration of autologous dendritic cell-based immunotherapy in the standard of care treatment for patients with newly diagnosed glioblastoma: results of the HGG-2006 phase I/II trial.

Autori: Ardon H., Van Gool SW., Verschuere T., Maes W., Fieuws S., Sciote R., Wilms G., Demaerel P., Goffin J., Van Calenbergh F., Menten J., Clement P., Debiec-Rychter M., De Vleeschouwer S.

Data di Pubblicazione: 2012-4-25

Abstract: Full integration of autologous DC-based tumor vaccination into standard postoperative radiochemotherapy for newly diagnosed glioblastoma seems safe and possibly beneficial. These results were used to power the currently running phase IIb randomized clinical trial.

Journal Title: Cancer immunology, immunotherapy : CII

PUBMED ID: 22464345

DOI: doi.org/10.1016/j.ejca.2012.02.004

Titolo: New prognostic factors and calculators for outcome prediction in patients with recurrent glioblastoma: a pooled analysis of EORTC Brain Tumour Group phase I and II clinical trials.

Autori: Gorlia T., Stupp R., Brandes AA., Rampling RR., Fumoleau P., Dittrich C., Campone MM., Twelves CC., Raymond E., Hegi ME., Lacombe D., van den Bent MJ.

Data di Pubblicazione: 2012-4-3

Abstract: This analysis confirms performance status but not age as a major prognostic factor for PFS and OS in recurrent GBM. Patients with multiple and

large lesions have an increased risk of death. With these data prognostic calculators with confidence intervals for both medians and fixed time probabilities of survival were derived.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 24031101

DOI: doi.org/10.3109/01658107.2012.658594

Titolo: None

Autori: Kang JJ., Hou JH., Bui KM., Michals E., Valyi-Nagy T., Koshy M., Munson T., Charbel FT., Villano JL., Moss HE.

Data di Pubblicazione: 2013-9-14

Abstract: Malignant optic nerve glioma (MONG) is a rare but uniformly fatal disease that remains poorly understood. We describe a notable case of this rare disease occurring in the optic chiasm. Normal brain imaging and normal ophthalmic examination two years prior to diagnosis provide evidence for

Journal Title: Neuro-ophthalmology (Aeolus Press)

PUBMED ID: 22461640

DOI: doi.org/10.1126/scitranslmed.3003016

Titolo: Anti-invasive adjuvant therapy with imipramine blue enhances chemotherapeutic efficacy against glioma.

Autori: Munson JM., Fried L., Rowson SA., Bonner MY., Karumbaiah L., Diaz B., Courtneidge SA., Knaus UG., Brat DJ., Arbiser JL., Bellamkonda RV.

Data di Pubblicazione: 2012-3-31

Abstract: The invasive nature of glioblastoma (GBM) represents a major clinical challenge contributing to poor outcomes. Invasion of GBM into healthy tissue restricts chemotherapeutic access and complicates surgical resection. Here, we test the hypothesis that an effective anti-invasive agent can "contain" GBM and increase the efficacy of chemotherapy. We report a new anti-invasive small molecule, Imipramine Blue (IB), which inhibits invasion of glioma in vitro when tested against several models. IB inhibits NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) oxidase-mediated reactive oxygen species generation and alters expression of actin regulatory elements. In vivo, liposomal IB (nano-IB) halts invasion of glioma, leading to a more compact tumor in an aggressively invasive RT2 syngeneic astrocytoma rodent model. When nano-IB therapy was followed by liposomal doxorubicin (nano-DXR) chemotherapy, the combination therapy prolonged survival compared to nano-IB or nano-DXR alone. Our data demonstrate that nano-IB-mediated containment of diffuse glioma enhanced the efficacy of nano-DXR chemotherapy, demonstrating the promise of an anti-invasive compound as an adjuvant treatment for glioma.

Journal Title: Science translational medicine

PUBMED ID: 22440872

DOI: doi.org/10.1016/j.nec.2012.01.004

Titolo: The role of BCNU polymer wafers (Gliadel) in the treatment of malignant glioma.

Autori: Nagpal S.

Data di Pubblicazione: 2012-3-24

Abstract: The 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU; carmustine) polymer wafer (Gliadel) was developed for use in malignant glioma to deliver higher doses of chemotherapy directly to tumor tissue while bypassing systemic side effects. Phase III clinical trials for patients with newly diagnosed malignant gliomas demonstrated a small, but statistically significant, improvement in survival. However, the rate of complications, including an increase in cerebrospinal fluid leaks and intracranial hypertension, has limited their use.

se. This article reviews the current data for use of BCNU wafers in malignant gliomas.

Journal Title: Neurosurgery clinics of North America

PUBMED ID: 22436661

DOI: doi.org/10.1186/1471-2407-12-99

Titolo: Phase I/IIa study of intratumoral/intracerebral or intravenous/intracerebral administration of Parvovirus H-1 (ParvOryx) in patients with progressive primary or recurrent glioblastoma multiforme: ParvOryx01 protocol.

Autori: Geletneky K., Huesing J., Rommelaere J., Schlehofer JR., Leuchs B., Dahm M., Krebs O., von Knebel Doeberitz M., Huber B., Hajda J.

Data di Pubblicazione: 2012-3-23

Abstract: ClinicalTrials.gov Identifier: NCT01301430.

Journal Title: BMC cancer

PUBMED ID: 22416109

DOI: doi.org/10.1093/neuonc/nos069

Titolo: Dynamic imaging response following radiation therapy predicts long-term outcomes for diffuse low-grade gliomas.

Autori: Pallud J., Llitjos JF., Dhermain F., Varlet P., Dezamis E., Devaux B., Souillard-Scémama R., Sanai N., Koziak M., Page P., Schlienger M., Daumas-Duport C., Meder JF., Oppenheim C., Roux FX.

Data di Pubblicazione: 2012-3-15

Abstract: Quantitative imaging assessment of radiation therapy (RT) for diffuse low-grade gliomas (DLGG) by measuring the velocity of diametric expansion (VDE) over time has never been studied. We assessed the VDE changes following RT and determined whether this parameter can serve as a prognostic factor. We reviewed a consecutive series of 33 adults with supratentorial DLGG treated with first-line RT with available imaging follow-up (median follow-up, 103 months). Before RT, all patients presented with a spontaneous tumor volume increase (positive VDE, mean 5.9 mm/year). After RT, all patients demonstrated a tumor volume decrease (negative VDE, mean, -16.7 mm/year) during a mean 49-month duration. In univariate analysis, initial tumor volume (>100 cm<sup>3</sup>), lack of IDH1 expression, p53 expression, high proliferation index, and fast post-RT tumor volume decrease (VDE at -10 mm/year or faster, fast responders) were associated with a significantly shorter overall survival (OS). The median OS was significantly longer (120.8 months) for slow responders (post-RT VDE slower than -10.0 mm/year) than for fast responders (47.9 months). In multivariate analysis, fast responders, larger initial tumor volume, lack of IDH1 expression, and p53 expression were independent poor prognostic factors for OS. A high proliferation index was significantly more frequent in the fast responder subgroup than in the slow responder subgroup. We conclude that the pattern of post-RT VDE changes is an independent prognostic factor for DLGG and offers a quantitative parameter to predict long-term outcomes. We propose to monitor individually the post-RT VDE changes using MRI follow-up, with particular attention to fast responders.

Journal Title: Neuro-oncology

PUBMED ID: 22402322

DOI: doi.org/10.1038/gt.2012.12

Titolo: Neural stem cell-mediated CE/CPT-11 enzyme/prodrug therapy in transgenic mouse model of intracerebellar medulloblastoma.

Autori: Gutova M., Shackelford GM., Khankaldyyan V., Herrmann KA., Shi XH., Mittelholtz K., Abramyants Y., Blanchard MS., Kim SU., Annala AJ., Najbauer J., Synold TW., D'Apuzzo M., Barish ME., Moats RA., Aboody KS.

Data di Pubblicazione: 2012-3-10

**Abstract:** Medulloblastoma is a heterogeneous diffuse neoplasm that can be highly disseminated, and is the most common malignant childhood brain tumor. Although multimodal treatments have improved survival rates for patients with medulloblastoma, these tumors are associated with high morbidity and mortality. New treatment strategies are urgently needed to improve cure rates and, importantly, to spare normal brain tissue from neurotoxicity and patients from life-long cognitive and functional deficits associated with current therapies. In numerous preclinical brain tumor models, neural stem cells (NSCs) have shown great promise as delivery vehicles for therapeutic genes. Here, we have used an established, genetically modified human NSC line (HB1.F3.CD) to deliver carboxylesterase (CE) to cerebellar tumor foci and locally activate the prodrug camptothecin-11 (CPT-11) (Irinotecan) to the potent topoisomerase I inhibitor SN-38. HB1.F3.CD NSC tumor tropism, intratumoral distribution and therapeutic efficacy were investigated in clinically relevant experimental models. Magnetic resonance imaging was used for in vivo tracking of iron nanoparticle-labeled NSCs, and to assess the therapeutic efficacy of CE-expressing HB1.F3.CD cells. As compared with controls, a significant decrease in tumor growth rate was seen in mice that received both NSCs and CPT-11 as the first treatment regimen. Thus, this study provides proof-of-concept for NSC-mediated CE/CPT-11 treatment of medulloblastoma, and serves as a foundation for further studies toward potential clinical application.

**Journal Title:** Gene therapy

PUBMED ID: 22396071

DOI: doi.org/10.1007/s11060-012-0832-5

**Titolo:** Dose dense 1 week on/1 week off temozolomide in recurrent glioma: a retrospective study.

**Autori:** Taal W., Segers-van Rijn JM., Kros JM., van Heuvel I., van der Rijt CC., Bromberg JE., Sillevius Smitt PA., van den Bent MJ.

**Data di Pubblicazione:** 2012-3-8

**Abstract:** Alternative temozolomide regimens have been proposed to overcome O(6)-methylguanine-DNA methyltransferase mediated resistance. We investigated the efficacy and tolerability of 1 week on/1 week off temozolomide (ddTMZ) regimen in a cohort of patients treated with ddTMZ between 2005 and 2011 for the progression of a glioblastoma during or after chemo-radiation with temozolomide or a recurrence of another type of glioma after radiotherapy and at least one line of chemotherapy. Patients received ddTMZ at 100-150 mg/m<sup>2</sup>/d (days 1-7 and 15-21 in cycles of 28-days). All patients had a contrast enhancing lesion on MRI and the response was assessed by MRI using the RANO criteria; complete and partial responses were considered objective responses. Fifty-three patients were included. The median number of cycles of ddTMZ was 4 (range 1-12). Eight patients discontinued chemotherapy because of toxicity. Two of 24 patients with a progressive glioblastoma had an objective response; progression free survival at 6 months (PFS-6) in glioblastoma was 29%. Three of the 16 patients with a recurrent WHO grade 2 or 3 astrocytoma or oligodendroglioma or oligo-astrocytoma without combined 1p and 19q loss had an objective response and PFS-6 in these patients was 38%. Four out of the 12 evaluable patients with a recurrent WHO grade 2 or 3 oligodendroglioma or oligo-astrocytoma with combined 1p and 19q loss had an objective response; PFS-6 in these patients was 62%. This study indicates that ddTMZ is safe and effective in recurrent glioma, despite previous temozolomide and/or nitrosourea chemotherapy. Our data do not suggest superior efficacy of this schedule as compared to the standard day 1-5 every 4 weeks schedule.

**Journal Title:** Journal of neuro-oncology

PUBMED ID: 22393086

DOI: doi.org/10.1200/JCO.2011.34.5843



Titolo: Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma.

Autori: Bouffet E., Jakacki R., Goldman S., Hargrave D., Hawkins C., Shroff M., Hukin J., Bartels U., Foreman N., Kellie S., Hilden J., Etzl M., Wilson B., Stephens D., Tabori U., Baruchel S.

Data di Pubblicazione: 2012-3-7

Abstract: Weekly vinblastine seems to be a reasonable alternative to radiation for pediatric patients with LGG who have experienced treatment failure with first-line chemotherapy. The 5-year progression-free survival observed in this phase II trial is comparable to results observed with first-line chemotherapy in chemotherapy-naïve patients. The role of single-agent vinblastine and other vinca alkaloid in the management of pediatric LGGs deserves further investigation.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 22371319

DOI: doi.org/10.1002/cncr.26541

Titolo: Phase II study of Gleevec plus hydroxyurea in adults with progressive or recurrent low-grade glioma.

Autori: Reardon DA., Desjardins A., Vredenburgh JJ., Herndon JE., Coan A., Gururangan S., Peters KB., McLendon R., Sathornsumetee S., Rich JN., Lipp ES., Janney D., Friedman HS.

Data di Pubblicazione: 2012-2-29

Abstract: Imatinib plus hydroxyurea was well tolerated among recurrent/progressive LGG patients but this regimen demonstrated negligible antitumor activity.

Journal Title: Cancer

PUBMED ID: 22364864

DOI: doi.org/10.1016/j.ophtha.2011.12.035

Titolo: Longitudinal measures of visual function, tumor volume, and prediction of visual outcomes after treatment of optic pathway gliomas.

Autori: Kelly JP., Leary S., Khanna P., Weiss AH.

Data di Pubblicazione: 2012-2-28

Abstract: The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Journal Title: Ophthalmology

PUBMED ID: 22341931

DOI: doi.org/10.1016/j.clineuro.2012.01.030

Titolo: Marked response of gliomatosis cerebri to temozolomide and whole brain radiotherapy.

Autori: Mattox AK., Lark AL., Adamson DC.

Data di Pubblicazione: 2012-2-21

Abstract: Gliomatosis cerebri (GC) represents an unfortunate, rare variant of glioma with a very poor prognosis. Given this lesion's rarity, little information exists on appropriate treatment options. The diffuse, infiltrative nature of GC precludes any surgical resection and limits therapy. Because of the improved survival seen with the use of temozolomide (TMZ) in malignant glioma, a rigorous systematic review of the published literature was performed to ascertain the benefit of TMZ in GC. We identified all GC cases in the literature where there was enough information to ascertain a clear response to a specific chemoradiotherapeutic treatment. In addition to our experience with a recent case, we have identified 61 patients with GC in the published literature who demonstrated a positive radiographic or clinic response after treatment. Statistical analysis of survival was performed by Kaplan-Meier and

alysis. A positive radiographic and clinical response was seen in patients ranging in age from 4 to 84 years. Overall median survival in patients diagnosed with GC who demonstrated a response after treatment was 25 months, with 1- and 2-year survival rates of 89% and 55%, respectively. The most common treatment regimens for responders included TMZ alone (26.2%), external whole-brain radiotherapy (WBRT) (26.2%), and concomitant TMZ and WBRT (20%). Our patient was treated with concomitant TMZ (150 mg/m<sup>2</sup>/day over 5 days) and WBRT (50 Gy) and has remained with a complete radiographic response after 36 months. In conclusion, patients with GC confirmed by surgical biopsy should be aggressively treated with concomitant TMZ and WBRT, as marked responses have been seen, and this appears to offer overall survival benefit.  
Journal Title: Clinical neurology and neurosurgery

PUBMED ID: 22322851

DOI: doi.org/10.1700/1018.11101

Titolo: Bone marrow metastases from anaplastic oligodendroglioma presenting with pancytopenia and hypogammaglobulinemia: a case report.

Autori: Cordiano V., Miserocchi F., Storti M.

Data di Pubblicazione: 2012-2-11

Abstract: We report the case of a 40-year-old man whose bone marrow metastases occurred 57 months after the initial diagnosis and 9 months after completing radiotherapy for an anaplastic oligodendroglioma. Four months before the demonstration of visceral metastases was obtained by bone marrow biopsy, the patient developed diffuse bone pain, pancytopenia, hypercalcemia, and panhypogammaglobulinemia. These abnormalities and other clinical signs of extracranial dissemination of the primary brain tumor were initially unrecognized until the patient was admitted with the suspicion of a nonsecretory multiple myeloma. We also briefly review the factors predisposing these tumors to spread outside the CNS, albeit rarely, and discuss the clinical implications of a misdiagnosis of extracranial invasion by anaplastic oligodendroglioma, whose chemosensitivity has been definitively demonstrated.

Journal Title: Tumori

PUBMED ID: 22268382

DOI: doi.org/10.2174/156800912799277557

Titolo: Targeting EGFR for treatment of glioblastoma: molecular basis to overcome resistance.

Autori: Taylor TE., Furnari FB., Cavenee WK.

Data di Pubblicazione: 2012-1-25

Abstract: Glioblastoma (glioblastoma multiforme; GBM; WHO Grade IV) accounts for the majority of primary malignant brain tumors in adults. Amplification and mutation of the epidermal growth factor receptor (EGFR) gene represent signature genetic abnormalities encountered in GBM. A range of potential therapies that target EGFR or its mutant constitutively active form, ΔEGFR, including tyrosine kinase inhibitors (TKIs), monoclonal antibodies, vaccines, and RNA-based agents, are currently in development or in clinical trials for the treatment of GBM. Data from experimental studies evaluating these therapies have been very promising; however, their efficacy in the clinic has so far been limited by both upfront and acquired drug resistance. This review discusses the current status of anti-EGFR agents and the recurrent problem of resistance to these agents that strongly indicates that a multiple target approach will provide a more favorable future for these types of targeted therapies in GBM.

Journal Title: Current cancer drug targets

PUBMED ID: 22214463

DOI: doi.org/10.2174/092986712799320646

Titolo: Efficacy and safety of bevacizumab in glioblastomas.

Autori: De Fazio S., Russo E., Ammendola M., Donato Di Paola E., De Sarro G.

Data di Pubblicazione: 2012-1-5

Abstract: Glioblastoma multiforme (GBM) is a common and malignant primary brain tumor arising from glial precursors the survival of which is estimated to be about 14 months after diagnosis despite current standard care with radiotherapy, surgery, and chemotherapies. Therapeutic approaches were greatly improved in the last years; however, GBM still represents the most lethal subtype of glioma. Actually, it has been estimated that only about 3.4% of patients will survive at the most five years when obtaining the best outcome from treatment; however, this depends on tumor resistance, which is generally related to repairing radiation injury, and self-improving cell growth repair and survival. All GBMs recur after initial therapy, limiting patients' survival at 20-25% within 1 year after diagnosis of recurrent disease. Moreover, for recurrent GBM response rates are less than 10% (ranging from 5% to 9%), and progression free survival at 6-month (PFS-6) rates range between 9% and 28% (median 15%). The development of targeted therapy based on tumor vascular blockade led to the approval of bevacizumab for recurrent or progressive glioblastoma, since it was proven that this offers a new opportunity for patients suffering from this malignancy. Bevacizumab is a recombinant antivascular monoclonal antibody binding to circulating Vascular Endothelial Growth Factor (VEGF) preventing this cytokine from reaching its receptors (VEGFR1 and VEGFR2) on endothelium, resulting in an inhibition of cells proliferation and vessels sprouting. The aim of this review is to address bevacizumab mode of action in malignant gliomas and provide a summary on currently available data on efficacy and safety.

Journal Title: Current medicinal chemistry

PUBMED ID: 22159180

DOI: doi.org/10.2967/jnumed.111.092387

Titolo: 3'-deoxy-3'-18F-fluorothymidine PET and MRI for early survival predictions in patients with recurrent malignant glioma treated with bevacizumab.

Autori: Schwarzenberg J., Czernin J., Cloughesy TF., Ellingson BM., Pope WB., Geist C., Dahlbom M., Silverman DH., Satyamurthy N., Phelps ME., Chen W.

Data di Pubblicazione: 2011-12-14

Abstract: Changes in tumor (18)F-FLT uptake were highly predictive of progression-free and overall survival in patients with recurrent malignant glioma on bevacizumab therapy. (18)F-FLT PET seems to be more predictive than MRI for early treatment response.

Journal Title: Journal of nuclear medicine : official publication, Society of Nuclear Medicine

PUBMED ID: 22158493

DOI: doi.org/10.1700/989.10721

Titolo: Treatment of recurrent high-grade gliomas with GliSite brachytherapy: a prospective mono-institutional Italian experience.

Autori: Gobitti C., Borsatti E., Arcicasa M., Roncadin M., Franchin G., Minatel E., Skrap M., Zanotti B., Tuniz F., Cimitan M., Capra E., Drigo A., Trovò MG.

Data di Pubblicazione: 2011-12-14

Abstract: Patients with recurrent high-grade glioma can be treated with additional surgery and GliSite brachytherapy, delivering 4500 cGy at 1 cm depth without significant acute side effects but with a significant rate (20%) of late radiation necrosis, resulting in 13% of treatment-related deaths. Compared with the literature, survival results in our study appear to be satisfactory, but they may be related to patient selection criteria. Re-intervention followed by GliSite brachytherapy should not be offered as a standard treat

ment for recurrent high-grade glioma, because of the high rate of late complications, treatment-related deaths, and high treatment costs.  
Journal Title: Tumori

PUBMED ID: 22145948

DOI: doi.org/10.1186/1746-1596-6-119

Titolo: Intraventricular glioneuronal tumor with disseminated lesions at diagnosis--a case report.

Autori: Yano H., Nakayama N., Hirose Y., Ohe N., Shinoda J., Yoshimura S., Iwama T.

Data di Pubblicazione: 2011-12-8

Abstract: A 55-year-old man presented with a large tumor in his lateral ventricles. Magnetic resonance imaging revealed disseminated lesions in the third and fourth ventricles at the time of diagnosis. The patient underwent a partial removal of the tumor in the lateral ventricles. Histologically, the surgical specimens showed glioneuronal differentiation with ganglion or ganglioid cells, Rosenthal fibers, oligodendroglia-like honeycomb appearances, a spongy pattern, perivascular pseudorosettes, and many hyalinized blood vessels. Papillary structure was not observed. The neuronal component showed a moderately high labeling index of Ki-67/MIB-1. We diagnosed this tumor as atypical intraventricular glioneuronal tumor. The disseminated lesions disappeared after chemoradiation therapy with temozolomide, and the residual tumors in the lateral ventricles remained stable for 3 years after the surgery. We discuss the pathological diagnosis, therapy and clinical course with review of the literatures.

Journal Title: Diagnostic pathology

PUBMED ID: 22117160

DOI: doi.org/10.1586/era.11.103

Titolo: Towards personalized therapy for patients with glioblastoma.

Autori: Shirai K., Chakravarti A.

Data di Pubblicazione: 2011-11-26

Abstract: Combined therapy with temozolomide and radiotherapy is a standard treatment and improves the survival for patients with newly diagnosed glioblastoma. However, the prognosis remains poor, with a median survival time of 12-15 months. Currently, several clinical trials of dose-dense temozolomide regimen or molecular-targeting therapies have been performed to overcome the resistance of glioblastoma. In these therapies, rational prognostic biomarkers have also been investigated to predict their outcome and response to treatment. This advanced understanding of the biological markers can help to develop personalized therapies for glioblastoma patients. Generally, due to a reduced tolerance, elderly patients do not seem to benefit from intensive treatment. This population needs individual treatments depended on their age or performance status. In this article, we review the recent studies that can provide personalized therapy for glioblastoma, based on molecular tumor profiling or patients' physical status.

Journal Title: Expert review of anticancer therapy

PUBMED ID: 22104357

DOI: doi.org/10.1016/j.ijrobp.2011.06.1952

Titolo: Experience with carbon ion radiotherapy for WHO Grade 2 diffuse astrocytomas.

Autori: Hasegawa A., Mizoe JE., Tsujii H., Kamada T., Jingu K., Iwadata Y., Nakazato Y., Matsutani M., Takakura K., Takakura K.

Data di Pubblicazione: 2011-11-23

Abstract: High-dose group patients showed significant improvement in PFS and OS rates compared to those in the low-dose group, and both dose groups showed acceptable toxicity.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 22101221

DOI: doi.org/10.1016/j.cct.2011.10.010

Titolo: A phase I trial of carboplatin administered by convection-enhanced delivery to patients with recurrent/progressive glioblastoma multiforme.

Autori: White E., Bienemann A., Taylor H., Hopkins K., Cameron A., Gill S.

Data di Pubblicazione: 2011-11-22

Abstract: Glioblastoma multiforme (GBM) is the commonest primary malignant brain tumour in adults. Standard treatment comprises surgery, radiotherapy and chemotherapy; however this condition remains incurable as these tumours are highly invasive and involve critical areas of the brain making it impossible to remove them surgically or cure them with radiotherapy. In the majority of cases the tumour recurs within 2 to 3 cm of the original site of tumour resection. Furthermore, the blood-brain barrier profoundly limits the access of many systemically administered chemotherapeutics to the tumour. Convection-enhanced delivery (CED) is a promising technique of direct intracranial drug delivery involving the implantation of microcatheters into the brain. Carboplatin represents an ideal chemotherapy to administer using this technique as glioblastoma cells are highly sensitive to carboplatin in vitro at concentrations that are not toxic to normal brain in vivo. This protocol describes a single-centre phase I dose-escalation study of carboplatin administered by CED to patients with recurrent or progressive GBM despite full standard treatment. This trial will incorporate 6 cohorts of 3 patients each. Cohorts will be treated in a sequential manner with increasing doses of carboplatin, subject to dose-limiting toxicity not being observed. This protocol should facilitate the identification of the maximum-tolerated infused concentration of carboplatin by CED into the supratentorial brain. This should facilitate the safe application of this technique in a phase II trial, treating patients with GBM, as well as for the treatment of other forms of malignant brain tumours, including metastases.

Journal Title: Contemporary clinical trials

PUBMED ID: 22076316

DOI: doi.org/10.1007/s10014-011-0070-0

Titolo: Adult cerebellar glioblastoma cases have different characteristics from supratentorial glioblastoma.

Autori: Utsuki S., Oka H., Miyajima Y., Kijima C., Yasui Y., Fujii K.

Data di Pubblicazione: 2011-11-15

Abstract: This study is a histological and clinical investigation of four cases of cerebellar glioblastoma, a rare tumor. The cases included three males and one female, from 33 to 67 years in age (mean 49 years). Tumor resection, postoperative irradiation and chemotherapy were performed in all cases. Two patients died of local tumor recurrence after 14 and 27 months. Another patient relapsed after 10 months; however, after additional tumor resection and second line chemotherapy, she remains disease-free 41 months after the initial treatment. The fourth patient has not relapsed in the 6 months since initial treatment. The histopathology of all cases was glioblastoma with pseudopalisading necrosis. However, low-grade glioma histopathology was found in three patients. All glioblastomas were immunopositive for p53 and immunonegative for epidermal growth factor receptor (EGFR) and isocitrate dehydrogenase 1 (IDH1). These adult cerebellar glioblastoma cases had similar clinical and pathological characteristics, and had different characteristics compared with supratentorial glioblastomas.

Journal Title: Brain tumor pathology

PUBMED ID: 22059142

DOI: doi.org/10.4103/2152-7806.86226

Titolo: Rare case of intracranial Salmonella enteritidis abscess following glioblastoma resection: Case report and review of the literature.

Autori: Sait M., Rahmathulla G., Chen TL., Barnett GH.

Data di Pubblicazione: 2011-11-8

Abstract: Re-operative tumor surgery has a higher incidence of post-operative infections, with Gram positive cocci being the most common pathogens. Predisposing factors reported for intracranial salmonellosis include compromised immunity, diabetes, HIV, and recent travel. Chronic corticosteroid use, multiple regimens of chemotherapy, and regions of tumor necrosis likely potentiate this rare infection in GBM patients.

Journal Title: Surgical neurology international

PUBMED ID: 22057917

DOI: doi.org/10.1007/s11060-011-0744-9

Titolo: Salvage gamma knife stereotactic radiosurgery followed by bevacizumab for recurrent glioblastoma multiforme: a case-control study.

Autori: Park KJ., Kano H., Iyer A., Liu X., Niranjan A., Flickinger JC., Lieberman FS., Lunsford LD., Kondziolka D.

Data di Pubblicazione: 2011-11-8

Abstract: We evaluated the efficacy and safety of gamma knife stereotactic radiosurgery (GKSR) followed by bevacizumab combined with chemotherapy in 11 patients with recurrent glioblastoma multiforme who experienced tumor progression despite aggressive initial multi-modality treatment. Our experience included eight male and three female patients. The median patient age at GKSR was 62 years (range 46-72 years). At the time of GKSR, seven patients had a first recurrence and four had two or more recurrences. The median interval from the initial diagnosis until GKSR was 17 months (range 5-34.5 months). The median tumor volume was 13.6 cm<sup>3</sup> (range 1.2-45.1 cm<sup>3</sup>) and the median margin dose of GKSR was 16 Gy (range 13-18 Gy). Following GKSR, bevacizumab was administered with irinotecan in nine patients and with temozolomide in one patient. One patient was treated with bevacizumab monotherapy. The treatment outcomes were compared to 44 case-matched controls who underwent GKSR without additional bevacizumab. At a median of 13.7 months (range 4.6-28.3 months) after radiosurgery, tumor progression was evident in seven patients. The median progression-free survival (PFS) was 15 months (95% confidential interval (CI), 6.5-23.3 months). Six-month and 1-year PFS rates were 73 and 55%, respectively. The median overall survival (OS) from GKSR was 18 months (95% CI, 10.1-25.7 months) and 1-year OS rate was 73%. One patient (9%) experienced grade III toxicity and one patient (9%) had major adverse radiation effects. Compared with patients who did not receive bevacizumab, the patients who received bevacizumab had significantly prolonged PFS (15 months vs. 7 months, P = 0.035) and OS (18 months vs. 12 months, P = 0.005), and were less likely to develop an adverse radiation effect (9 vs. 46%, P = 0.037). The combination of salvage GKSR followed by bevacizumab added potential benefit and little additional risk in a small group of patients with progressive glioblastoma. Further experience is needed to define the efficacy and long-term toxicity with this strategy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 22044816

DOI: doi.org/10.4103/0973-1482.87039

Titolo: Invasion is not an independent prognostic factor in high-grade glioma.

Autori: Narayana A., Perretta D., Kunnakkat S., Gruber D., Golfinos J., Parker E., Medabalmi P., Zagzag D., Pat Eagan RN., Gruber M.

Data di Pubblicazione: 2011-11-3

Abstract: Presence of diffuse invasive disease not accompanied by angiogenesis is either prior to therapy or subsequent to anti-angiogenic therapy does not seem to have prognostic significance. However, invasion accompanied by angiogenesis in newly diagnosed HGG may confer a poor prognosis.

Journal Title: Journal of cancer research and therapeutics

PUBMED ID: 22035272

DOI: doi.org/10.3171/2011.9.JNS11656

Titolo: A clinical trial of bevacizumab, temozolomide, and radiation for newly diagnosed glioblastoma.

Autori: Narayana A., Gruber D., Kunnakkat S., Golfinos JG., Parker E., Raza S., Zagzag D., Eagan P., Gruber ML.

Data di Pubblicazione: 2011-11-1

Abstract: The addition of bevacizumab to conventional therapy in newly diagnosed GBM appears to improve both PFS and OS in patients with newly diagnosed GBM, with acceptable morbidity. A shift toward diffuse relapse was noted in a significant number of patients. Ongoing Phase III clinical trials will show the true benefit of this antiangiogenic approach.

Journal Title: Journal of neurosurgery

PUBMED ID: 21993440

DOI: doi.org/10.1093/neuonc/nor173

Titolo: Low-dose fractionated radiotherapy and concomitant chemotherapy in glioblastoma multiforme with poor prognosis: a feasibility study.

Autori: Balducci M., Chiesa S., Diletto B., D'Agostino GR., Mangiola A., Manfreda S., Mantini G., Albanese A., Fiorentino A., Frascino V., De Bari B., Micciche' F., De Rose F., Morganti AG., Anile C., Valentini V.

Data di Pubblicazione: 2011-10-14

Abstract: We explored the feasibility of concurrent palliative chemotherapy and low-dose fractionated radiotherapy (LD-FRT) in glioblastoma multiforme (GBM). Patients with recurrent/progressive GBM at least 3 months after the end of primary radiotherapy received 0.3 Gy twice daily with cisplatin and fotemustine if progressing on temozolomide, or 0.4 Gy twice daily with temozolomide if recurrent 4-6 months later (retreatment group). Newly diagnosed GBM with gross residual mass received 30 Gy with concomitant and adjuvant temozolomide and 0.4 Gy twice daily from the second adjuvant cycle (naive group) for 2-4 cycles. Twenty-six patients were enrolled. In the retreatment group (n = 17; median LD-FRT total dose 7.2 Gy [range 2.4-11.6]), grade 3 or 4 hematological toxicity was observed in 5.9% of patients. Median follow-up time was 20 months (range 4-35). Median progression-free survival (PFS) and overall survival (OS) from the time of recurrence or progression were 4 and 8 months, respectively (OS at 6 months, 69%; at 12 months, 16.7%). In the naive group (n = 9; median LD-FRT total dose 8 Gy [range 3.2-16]), grade 3 or 4 hematological toxicity was observed in 11.1% of patients. Median follow-up time was 17 months (range 8-20)-median PFS was 9 months, with PFS at 6 months and at 1 year of 66.7% and 26.7%, respectively; and median OS was 12 months, with OS at 6 months and at 1 year of 77.8% and 34.6%, respectively. LD-FRT with concurrent chemotherapy was well tolerated.

Journal Title: Neuro-oncology

PUBMED ID: 21986722

DOI: doi.org/10.1007/s11060-011-0722-2

Titolo: Phase II study of carboplatin, irinotecan, and bevacizumab for bevacizumab naïve, recurrent glioblastoma.

Autori: Reardon DA., Desjardins A., Peters KB., Gururangan S., Sampson JH., McLendon RE., Herndon JE., Bulusu A., Threatt S., Friedman AH., Vredenburgh JJ., Friedman HS.

Data di Pubblicazione: 2011-10-12

Abstract: We evaluated the efficacy of carboplatin, irinotecan, and bevacizumab among bevacizumab-naïve, recurrent glioblastoma (GBM) patients in a phase 2, open-label, single arm trial. Forty eligible patients received carboplatin (area under the plasma curve [AUC] 4 mg/ml-min) on day one, while bevacizumab (10 mg/kg) and irinotecan (340 mg/m<sup>2</sup>) for patients on CYP3A-enzyme-inducing anti-epileptics [EIAEDs] and 125 mg/m<sup>2</sup>) for patients not on EIAEDs) were administered on days 1 and 14 of every 28-day cycle. Patients were evaluated after each of the first two cycles and then after every other cycle. Treatment continued until progressive disease, unacceptable toxicity, non-compliance, or voluntary withdrawal. The primary endpoint was progression-free survival at 6 months (PFS-6) and secondary endpoints included safety and median overall survival (OS). All patients had progression after standard therapy. The median age was 51 years. Sixteen patients (40%) had a KPS of 90-100, while 27 (68%) were at first progression. The median time from original diagnosis was 11.4 months. The PFS-6 rate was 46.5% (95% CI: 30.4, 61.0%) and the median OS was 8.3 months [95% confidence interval (CI): 5.9, and 10.7 months]. Grade 4 events were primarily hematologic and included neutropenia and thrombocytopenia in 20 and 10%, respectively. The most common grade 3 events were neutropenia, thrombocytopenia, fatigue, and infection in 25, 20, 13, and 10%, respectively. Eleven patients (28%) discontinued study therapy due to toxicity and 17 patients (43%) required dose modification. One patient died due to treatment-related intestinal perforation. The addition of carboplatin and irinotecan to bevacizumab significantly increases toxicity but does not improve anti-tumor activity to that achieved historically with single-agent bevacizumab among bevacizumab-naïve, recurrent GBM patients. (ClinicalTrials.gov number NCT00953121).

Journal Title: Journal of neuro-oncology

PUBMED ID: 21984222

DOI: doi.org/10.1007/s00280-011-1754-1

Titolo: Pharmacokinetic drug interaction between AEE788 and RAD001 causing thrombocytopenia in patients with glioblastoma.

Autori: Reardon DA., Cloughesy T., Rich J., Alfred Yung WK., Yung L., DiLea C., Huang J., Dugan M., Mietlowski W., Maes A., Conrad C.

Data di Pubblicazione: 2011-10-11

Abstract: The coadministration of AEE788 and RAD001 in glioblastoma patients caused a clinically significant thrombocytopenia and a higher-than-expected RAD001 area under the curve concentration when dosed at 200 and 5 mg/day, respectively. After a dose reduction to AEE788 (150 mg/day) and RAD001 (5 mg qod), the combination appeared to be better tolerated.

Journal Title: Cancer chemotherapy and pharmacology

PUBMED ID: 21982454

DOI: doi.org/10.1186/1471-2407-11-432

Titolo: A phase I trial of PR-104, a pre-prodrug of the bioreductive prodrug PR-104A, given weekly to solid tumour patients.

Autori: McKeage MJ., Gu Y., Wilson WR., Hill A., Amies K., Melink TJ., Jameson MB.

Data di Pubblicazione: 2011-10-11

Abstract: Thrombocytopenia, and to a lesser extent neutropenia, was the DLT of weekly PR-104. The MTD was 675 mg/m<sup>2</sup>/week. PR-104 given weekly may be a suitable protocol for further clinical evaluation as a short course of treatment with fractionated radiotherapy or haematopoietic stem cell support, as i



ts duration of dosing is restricted by delayed-onset and protracted thrombocytopenia.

Journal Title: BMC cancer

PUBMED ID: 21975337

DOI: doi.org/10.1007/s12094-011-0726-6

Titolo: A safety and toxicity assessment of the administration of multiple intracerebral injections of irinotecan or doxorubicin drug-eluting beads.

Autori: Held N., Lewis AL., Hedrich HJ., Brinker T., Glage S.

Data di Pubblicazione: 2011-10-7

Abstract: OBJECTIVE Previous research in a rat glioma model has shown that the local intratumoral application of polymerbased drug-eluting beads (DEBs) loaded with doxorubicin or irinotecan suppress tumour growth and prolong survival. For translation into a clinical setting, the present experiment investigates in the healthy cat brain the local and systemic toxicity of a multiple injection shot technique. METHODS Three injection shots were placed, each at a 1 cm distance in the frontal lobe. The DEBs were suspended in an aqueous alginate excipient solution, which becomes subject to a sol-gel transition when injected into the Ca(2+)-rich brain tissue environment. Systemic and local side effects were monitored over a period of two weeks. Injection sites were histologically investigated. RESULTS Gelling of the alginate results in the permanent immobilisation of the microspheres at the implantation site. A distinct local cytotoxic effect of doxorubicin was found with intracerebral and intraventricular haemorrhages, and signs of brain tissue necrosis. In cats injected with irinotecan DEBs, such local adverse side effects did not occur. No signs of systemic toxicity were found with both chemotherapeutics. DISCUSSION We conclude that the multiple injection shot technique with irinotecan DEBs meets feasibility criteria and safety requirements for a clinical application.

Journal Title: Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico

PUBMED ID: 21969508

DOI: doi.org/10.1200/JCO.2011.37.3381

Titolo: Stereotactic brachytherapy with iodine-125 seeds for the treatment of inoperable low-grade gliomas in children: long-term outcome.

Autori: Ruge MI., Simon T., Suchorska B., Lehrke R., Hamisch C., Koerber F., Maarouf M., Treuer H., Berthold F., Sturm V., Voges J.

Data di Pubblicazione: 2011-10-5

Abstract: We demonstrate that SBT represents a safe, minimally invasive, and highly effective local treatment option for pediatric patients with inoperable LGG WHO grades I and II.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 21968944

DOI: doi.org/10.1007/s11060-011-0721-3

Titolo: O<sup>6</sup>-methylguanine-DNA methyltransferase promoter methylation in 45 primary central nervous system lymphomas: quantitative assessment of methylation and response to temozolomide treatment.

Autori: Adachi J., Mishima K., Wakiya K., Suzuki T., Fukuoka K., Yanagisawa T., Matsutani M., Sasaki A., Nishikawa R.

Data di Pubblicazione: 2011-10-5

Abstract: Favorable responses to temozolomide chemotherapy have recently been reported in primary central nervous system lymphoma (PCNSL) patients who a

re refractory to high-dose methotrexate therapy. The gene encoding the DNA repair enzyme O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) is transcriptionally silenced by promoter methylation in several human tumors, including gliomas and systemic lymphomas. MGMT promoter methylation is also a prognostic marker in glioblastoma patients treated with temozolomide. To validate temozolomide treatment in PCNSL, we applied methylation-sensitive high resolution melting (MS-HRM) analysis to quantitate MGMT methylation in PCNSL. MGMT promoter methylation was detected in tumors from 23 (51%) of 45 PCNSL patients, 11 of which were considered to have high (more than 70.0%) methylation status. Of the five recurrent PCNSLs treated with temozolomide, four cases responded, with three achieving complete response and one, a partial response. All four responsive PCNSLs had methylated MGMT promoters, whereas the non-responsive recurrent PCNSL did not. Thus, the use of quantitative MS-HRM analysis for the detection of MGMT promoter methylation has been suggested in PCNSL for the first time. The assay allows rapid and high-throughput evaluation of the MGMT methylation status, and seems to be promising in clinical settings. MGMT promoter methylation may become a useful marker for predicting the response of PCNSLs to temozolomide.

Journal Title: Journal of neuro-oncology

PUBMED ID: 21961538

DOI: doi.org/10.3171/2011.7.PEDS11179

Titolo: Concomitant intraventricular colloid cyst and low-grade astrocytoma of the brainstem in a 16-year-old boy.

Autori: Amirjamshidi A., Amiri RS., Alimohamadi M., Abbassioun K.

Data di Pubblicazione: 2011-10-4

Abstract: Multiple primary brain tumors are commonly observed in patients with a history of brain radiation therapy or neurofibromatosis. The concomitant presence of 2 different types of brain tumors in a single location or chamber is a very rare clinical presentation in the absence of such a predisposing factor. The authors report on the case of a 16-year-old boy presenting with different types of brain tumors in 2 ventricular chambers concomitantly. This boy had a medium-sized colloid cyst of the third ventricle and a large fibrillary astrocytoma fungating from the brainstem into the floor of the fourth ventricle. The lesions were successfully excised in 2 separate surgeries. Radiotherapy was used as the adjuvant mode of therapy. There has been no sign of tumor recurrence after 16 months of follow-up. Clinical awareness and recognition of such a combination of tumors is important because they will dictate special treatment strategies depending on the individual biological aggressiveness of each tumor.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 21954442

DOI: doi.org/10.1093/neuonc/nor145

Titolo: Phase I trial of sorafenib in patients with recurrent or progressive malignant glioma.

Autori: Nabors LB., Supko JG., Rosenfeld M., Chamberlain M., Phuphanich S., Batchelor T., Desideri S., Ye X., Wright J., Gujar S., Grossman SA., Grossman SA.

Data di Pubblicazione: 2011-9-29

Abstract: Sorafenib is an inhibitor of multiple kinases that has demonstrated antiproliferative and antiangiogenic activity in a number of in vitro and in vivo model systems. A phase I study was conducted to determine the maximum tolerated dose (MTD) of sorafenib in patients with recurrent malignant glioma. Sorafenib was given orally, twice a day (BID), continuously in 28-day cycles. The dose was escalated in 2 groups of patients stratified by use of enzyme-inducing antiseizure drugs ( $\pm$  EIASDs). Dose-limiting toxicity (DLT) was defined as any grades 3-4 nonhematological toxicity, grade 4 hematological

toxicity, and febrile neutropenia. The number of evaluable patients enrolled in the +EIASD and -EIASD arms were 23 and 24, respectively. DLTs were predominantly dermatological and gastrointestinal effects, as observed in previous clinical trials of sorafenib. The MTD was 600 mg BID for patients receiving EIASDs and 800 mg BID for those who were not. The plasma pharmacokinetics of sorafenib were not significantly affected by the concurrent administration of EIASDs. The MTD of sorafenib given orally BID on a continuous basis was established as 600 mg BID in patients with malignant glioma who were concurrently receiving EIASDs and 800 mg BID in those who were not. Further evaluation is warranted of sorafenib at the recommended MTD against recurrent or progressive malignant glioma in combination with other molecularly targeted drugs or in the newly diagnosed setting concurrent with chemoradiation.  
Journal Title: Neuro-oncology

PUBMED ID: 21943399

DOI: doi.org/10.1186/1748-717X-6-121

Titolo: Evaluation of early imaging response criteria in glioblastoma multiforme.

Autori: Gladwish A., Koh ES., Hoisak J., Lockwood G., Millar BA., Mason W., Yu E., Laperriere NJ., Ménard C.

Data di Pubblicazione: 2011-9-28

Abstract: We show that while a subjective interpretation of early radiological progression from baseline is generally associated with poor outcome, true progressors cannot be distinguished from pseudoprogressors. In contrast, the magnitude of early imaging volumetric response may be a predictive and quantitative metric of favorable outcome.

Journal Title: Radiation oncology (London, England)

PUBMED ID: 21909069

DOI: Mancante

Titolo: [Neurofibromatosis type 1 and hypertension in pediatrics: case report].

Autori: Demarchi I., Genoni G., Prodam F., Petri A., Busti A., Cortese L., Negro M., Bellone S., Acucella G., Bona G.

Data di Pubblicazione: 2011-9-13

Abstract: Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder characterized by café-au-lait spots, axillary and inguinal freckling, cutaneous neurofibromas with a variable clinical expression, iris Lisch nodules, and multiple tumors, in particular optic nerve and other central nervous system gliomas. About 6% of patients develop hypertension due to renovascular diseases, mid-aortic syndrome, or pheochromocytoma. We present a case of a 8 year old girl with primary diagnosis of NF1 suffering of skin and encephalic neurofibromas, inguinal freckling, café-au-lait spots, optic nerve glioma, headache, facial flushing. The 24-h ambulatory blood pressure revealed hypertension without paroxysmal attacks. Urinary metanephrines, serum aldosterone, renin and kalemia were constantly normal. Magnetic resonance imaging (MRI) and a ngioMRI excluded stenoses of the renal arteries or adrenal masses. Standard 2D echocardiography was normal. The antihypertensive medication controlled pressure values. We concluded for hypertension due to a low-grade vasculopathy. The periodic monitoring of blood pressure in NF1 patients, accompanied by appropriate diagnostic modalities and physical examination, is essential to precociously diagnose hypertension and avoid life-threatening organ damages and increased mortality.

Journal Title: Minerva pediatrica

PUBMED ID: 23905037

DOI: Mancante

Titolo: Potential clinical role of telomere length in human glioblastoma.

Autori: La Torre D., Aguenouz M., Conti A., Giusa M., Raffa G., Abbritti RV., Germano A., Angileri FF.

Data di Pubblicazione: 2013-8-2

Abstract: Glioblastoma Multiforme (GBM) is the most common and lethal of human primary central nervous system (CNS) tumors. Due to the tumour's intrinsic clinical and molecular heterogeneity, choice of initial treatment, prediction of survival, stratification of patients, prediction and monitoring of response to therapy, represent some of the greatest challenges in the management of GBM patients. Patients, despite optimal surgery, radiation and chemotherapy, still have a median survival of 14-16 months. A reason for this dismal prognosis is because of the relative inaccuracy of current prognostic markers, so far based on clinical or pathological variables. Molecular markers that effectively predict response to therapy and survival outcomes are limited. Consequently, there is a strong need to develop novel and independent markers of prognosis. Ideal biomarkers for solid tumors would serve one or more important functions. Telomeres, guanine-rich tandem DNA repeats of the chromosomal end, provide chromosomal stability, regulates important cellular processes, and seem to be implicated in human carcinogenesis. Recently, telomeres have been shown either to be associated with clinical markers of disease progression or to be independent markers of cancer prognosis in solid tumours, including GBM. Nevertheless, a corresponding comprehensive discussion of these promising developments in brain tumours has not yet been available in the literature. Therefore, here we reviewed studies focused on the assessment of telomeric length in brain tumours with the aim to emphasize those findings indicating a potential clinical role of telomeres in GBM. With the aim to enhance the awareness of the potential clinical role of telomeres' length in formation in GBM, using a southern blot analysis, telomeric length in excised tumour samples was analyzed. Moreover, an attempt to correlate telomere length with patients' overall survival, was also performed. The findings here reviewed shows some contradictory results, due to different tissues used as controls, but mainly to cellular and molecular heterogeneity in GBMs that drive molecular mechanisms controlling telomere length, included telomerase and Alternative Lengthening of Telomeres (ALT), through multiple mechanisms. However, overall these studies, including our own, are consistent with the hypothesis that GBMs' telomeres were always shorter when compared with Normal Brain Tissue (NBT), and together with higher telomerase activity seem to be associated with malignancy and poor outcome; while tumours with ALT phenotype have longer telomeres, "less malignant" behaviour and better prognosis. We conclude that, although not entirely consistent in the type of telomere alteration, i.e., attrition vs. elongation, and unclear on the underlying mechanisms, multiple studies in brain tumours have shown that telomere dysfunction is associated with parameters of clinical outcome in patients with GBMs and therefore will be part of novel risk assessment and prognostic modalities for patients with these still dismal disease.

Journal Title: Translational medicine @ UniSa

PUBMED ID: 21870118

DOI: doi.org/10.1007/s11060-011-0698-y

Titolo: A phase II trial of thalidomide and procarbazine in adult patients with recurrent or progressive malignant gliomas.

Autori: Ruiz J., Case D., Enevold G., Rosdhal R., Tatter SB., Ellis TL., McQuellon RP., McMullen KP., Stieber VW., Shaw EG., Lesser GJ.

Data di Pubblicazione: 2011-8-27

Abstract: Thalidomide and procarbazine have demonstrated single agent activity against malignant gliomas (MG). We evaluated the combination of thalidomide and procarbazine with a single arm phase II trial in adults with recurrent or progressive MG. Procarbazine was given at a dose of 250 mg/m<sup>2</sup>/d × 5 days q 28 days. Thalidomide was administered at a dose of 200 mg/day continuous

ly. Inpatient dose escalation of thalidomide was attempted (increase by 100 mg/day weekly as tolerated) to a maximum of 800 mg/day. The primary outcome was tumor response, assessed by MRI and CT. Secondary outcomes were progression free survival (PFS), overall survival (OS) and toxicity. In addition, quality of life questionnaires were performed at baseline and prior to each odd cycle in all treated patients. Eighteen patients (median age of 50) were accrued and received a total of 36 cycles (median 2) of therapy. The median maximum thalidomide dose achieved was 400 mg (range 0-800). No complete or partial responses were seen. One patient (6%) experienced stable disease, fourteen (78%) progressed as best response and three (17%) were not evaluable for response. Median time to progression was 2.1 months (95% CI, 1.5-2.5). Seventeen patients have died (one patient lost to follow-up after progression); median survival from enrollment was 7.6 months (95% CI, 3.5-9.4). Grade 3/4 drug related toxicity was minimal. Quality of life diminished over time. The combination of thalidomide and procarbazine demonstrated no efficacy in this trial.

Journal Title: Journal of neuro-oncology

PUBMED ID: 21868412

DOI: doi.org/10.1093/neuonc/nor100

Titolo: Stereotactic brachytherapy of low-grade cerebral glioma after tumor resection.

Autori: Suchorska B., Ruge M., Treuer H., Sturm V., Voges J.

Data di Pubblicazione: 2011-8-27

Abstract: The purpose of this study was to assess the impact of stereotactic brachytherapy (SBT) on survival time and outcome when applied after resection of low-grade glioma (LGG) of World Health Organization grade II. From January 1982 through December 2006 we treated 1024 patients who had glioma with stereotactic implantation of iodine-125 seeds and SBT in accordance with a prospective protocol. For the present analysis, we selected 95 of 277 patients with LGG, in whom SBT was applied to treat progressive (43 patients) or recurrent (52 patients) tumor after resection. At 24 months after seed implantation, the tumor response rate was 35.9%, and the tumor control rate was 97.3%. The median progression-free-survival (PFS) duration after SBT was 52.7 ± 7.1 months. Five-year and 10-year PFS probabilities were 43.4% and 10.7%, respectively. Malignant tumor transformation, the diagnosis "astrocytoma," and tumor volume >20 mL were significantly associated with reduced PFS. Tumor progression or relapse after SBT (53 of 95 patients) was treated with tumor resection, a second SBT, chemotherapy, and/or radiotherapy. The median overall survival duration (from the first diagnosis of LGG until the patient's last contact) was 245.0 ± 4.9 months. Patients still under observation after seed implantation had a median follow-up time of 156.4 ± 55.7 months. Perioperative transient morbidity was 1.1%, and the frequency of permanent morbidity caused by SBT was 3.3%. In conclusion, SBT of recurrent or progressive LGG after resection located in functionally critical brain areas has high local efficacy and comparably low morbidity. Referred to individually adopted glioma treatment concepts SBT provides a reasonably long PFS, thus improving overall survival. In selected patients, SBT can lead to delays in the application of chemotherapy and/or radiotherapy.

Journal Title: Neuro-oncology

PUBMED ID: 21865400

DOI: doi.org/10.1093/neuonc/nor091

Titolo: A phase II trial of single-agent bevacizumab in patients with recurrent anaplastic glioma.

Autori: Kreisl TN., Zhang W., Odia Y., Shih JH., Butman JA., Hammoud D., Iwamoto FM., Sul J., Fine HA.

Data di Pubblicazione: 2011-8-26

**Abstract:** The purpose of this study was to evaluate the activity of single-agent bevacizumab in patients with recurrent anaplastic glioma and assess correlative advanced imaging parameters. Patients with recurrent anaplastic glioma were treated with bevacizumab 10 mg/kg every 2 weeks. Complete patient evaluations were repeated every 4 weeks. Correlative dynamic contrast-enhanced MR and (18)fluorodeoxyglucose PET imaging studies were obtained to evaluate physiologic changes in tumor and tumor vasculature at time points including baseline, 96 h after the first dose, and after the first 4 weeks of therapy. Median overall survival was 12 months (95% confidence interval [CI]: 6.08-22.8). Median progression-free survival was 2.93 months (95% CI: 2.01-4.93), and 6-month progression-free survival was 20.9% (95% CI: 10.3%-42.5%). Thirteen (43%) patients achieved a partial response. The most common grade  $\geq 3$  treatment-related toxicities were hypertension, hypophosphatemia, and thromboembolism. Single-agent bevacizumab produces significant radiographic response in patients with recurrent anaplastic glioma but did not meet the 6-month progression-free survival endpoint. Early change in enhancing tumor volume at 4 days after start of therapy was the most significant prognostic factor for overall and progression-free survival.

**Journal Title:** Neuro-oncology

PUBMED ID: 21859839

DOI: doi.org/10.1158/1535-7163.MCT-11-0268

**Titolo:** A molecular screening approach to identify and characterize inhibitors of glioblastoma stem cells.

**Autori:** Visnyei K., Onodera H., Damoiseaux R., Saigusa K., Petrosyan S., DeVries D., Ferrari D., Saxe J., Panosyan EH., Masterman-Smith M., Mottahedeh J., Bradley KA., Huang J., Sabatti C., Nakano I., Kornblum HI.

**Data di Pubblicazione:** 2011-8-24

**Abstract:** Glioblastoma (GBM) is among the most lethal of all cancers. GBM consists of a heterogeneous population of tumor cells among which a tumor-initiating and treatment-resistant subpopulation, here termed GBM stem cells, have been identified as primary therapeutic targets. Here, we describe a high-throughput small molecule screening approach that enables the identification and characterization of chemical compounds that are effective against GBM stem cells. The paradigm uses a tissue culture model to enrich for GBM stem cells derived from human GBM resections and combines a phenotype-based screen with gene target-specific screens for compound identification. We used 31,624 small molecules from 7 chemical libraries that we characterized and ranked based on their effect on a panel of GBM stem cell-enriched cultures and their effect on the expression of a module of genes whose expression negatively correlates with clinical outcome: MELK, ASPM, TOP2A, and FOXM1b. Of the 11 compounds meeting criteria for exerting differential effects across cell types used, 4 compounds showed selectivity by inhibiting multiple GBM stem cell-enriched cultures compared with nonenriched cultures: emetine, n-arachidonyl dopamine, n-oleoyldopamine (OLDA), and n-palmitoyl dopamine. ChemBridge compounds #5560509 and #5256360 inhibited the expression of the 4 mitotic module genes. OLDA, emetine, and compounds #5560509 and #5256360 were chosen for more detailed study and inhibited GBM stem cells in self-renewal assays in vitro and in a xenograft model in vivo. These studies show that our screening strategy provides potential candidates and a blueprint for lead compound identification in larger scale screens or screens involving other cancer types.

**Journal Title:** Molecular cancer therapeutics

PUBMED ID: 21858608

DOI: doi.org/10.1007/s11060-011-0677-3

**Titolo:** Treatment of recurrent diffuse intrinsic pontine glioma: the MD Anderson Cancer Center experience.

Autori: Wolff JE., Rytting ME., Vats TS., Zage PE., Ater JL., Woo S., Kuttelch J., Ketonen L., Mahajan A.

Data di Pubblicazione: 2011-8-23

Abstract: Recurrent diffuse intrinsic pontine gliomas (DIPG) are traditionally treated with palliative care since no effective treatments have been described for these tumors. Recently, clinical studies have been emerging, and individualized treatment is attempted more frequently. However, an informative way to compare the treatment outcomes has not been established, and historical control data are missing for recurrent disease. We conducted a retrospective chart review of patients with recurrent DIPG treated between 1998 and 2010. Response progression-free survival and possible influencing factors were evaluated. Thirty-one patients were identified who were treated in 61 treatment attempts using 26 treatment elements in 31 different regimens. The most frequently used drugs were etoposide (14), bevacizumab (13), irinotecan (13), nimotuzumab (13), and valproic acid (13). Seven patients had repeat radiation therapy to the primary tumor. Response was recorded after 58 treatment attempts and was comprised of 0 treatment attempts with complete responses, 7 with partial responses, 20 with stable diseases, and 31 with progressive diseases. The median progression-free survival after treatment start was 0.16 years (2 months) and was found to be correlated to the prior time to progression but not to the number of previous treatment attempts. Repeat radiation resulted in the highest response rates (4/7), and the longest progression-free survival. These data provide a basis to plan future clinical trials for recurrent DIPG. Repeat radiation therapy should be tested in a prospective clinical study.

Journal Title: Journal of neuro-oncology

PUBMED ID: 21858607

DOI: doi.org/10.1007/s11060-011-0681-7

Titolo: Radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma.

Autori: Chassot A., Canale S., Varlet P., Puget S., Roujeau T., Negretti L., Dhermain F., Rialland X., Raquin MA., Grill J., Dufour C.

Data di Pubblicazione: 2011-8-23

Abstract: The purpose of this study is to evaluate the efficacy and toxicity of radiation therapy (RT) with concurrent temozolomide (TMZ) chemotherapy followed by adjuvant TMZ in children with diffuse intrinsic pontine glioma (DIPG). Newly diagnosed patients younger than 18 years with histologically proven DIPG were treated with focal radiotherapy to a dose of 54 Gy in 30 fractions along with concurrent daily TMZ (75 mg/m<sup>2</sup>/day). Four weeks after completing the initial RT-TMZ schedule, adjuvant TMZ (200 mg/m<sup>2</sup>/day, days 1-5) was given every 28 days up to six cycles. Responses/progressions were assessed by clinical and 2-monthly MRI follow-up studies. Between September 2005 and September 2009, 21 patients with newly diagnosed histologically confirmed DIPG were eligible for this study. Median age at diagnosis was 6.4 years (range 4-16 years). At last update in August 2010, 17 children have died, 1 child was alive with progressive disease and 3 with stable disease. Metastatic relapse was documented in the cerebral site in two patients and in spinal cord in two cases. The median time to progression was 7.5 months (range 28 days-14.5 months) and the median survival was 11.7 months (range 26 days-17.5 months). The 1-year PFS and the 1-year OS were 33 and 50%, respectively. Five patients presented radiological findings compatible with pseudoprogression during the treatment. Haematological toxicity (Grade III/IV thrombocytopenia and leucopenia) was the most commonly found and led to dose reductions of TMZ in 58% of the patients. TMZ with radiation therapy has not yielded any significant improvement in outcome of children with DIPG and is associated with higher toxicity compared with radiotherapy alone. Novel treatment modalities are needed to improve the outcome of these patients.

Journal Title: Journal of neuro-oncology

PUBMED ID: 21845585

DOI: doi.org/10.5137/1019-5149.JTN.2947-10.0

Titolo: Cerebral tuberculoma mimicking high grade glial tumor.

Autori: Suslu HT., Bozbuga M., Bayindir C.

Data di Pubblicazione: 2011-8-17

Abstract: Tuberculosis has been an important public health problem in both developing and developed nations. Tuberculosis of the central nervous system is rare. Tuberculosis meningitis and tuberculoma are the two most important manifestations of tuberculosis of the CNS. Intracranial tuberculomas may be solitary or multiple. Solitary tuberculomas may be indistinguishable from cranial abscess or primary brain tumor. It is necessary to rule out tuberculoma in patients with intracranial mass lesions. We present a case of tuberculoma mimicking a high grade glial tumor on magnetic resonance imaging and clinical presentation. A 30-year-old woman presented with one-month history of epilepsy. Cranial magnetic resonance imaging showed a left occipital peripheral ring-enhanced lesion with central necrosis. There was a strong suspicion of glial tumor. The lesion was totally excised with left occipital craniotomy. Histological examination of mass revealed a tuberculoma. The patient was treated with antituberculous chemotherapy.

Journal Title: Turkish neurosurgery

PUBMED ID: 21842314

DOI: doi.org/10.1007/s11060-011-0674-6

Titolo: Oligodendrogliomas in children.

Autori: Creach KM., Rubin JB., Leonard JR., Limbrick DD., Smyth MD., Dacey R., Rich KM., Dowling JL., Grubb RL., Linette GP., King AA., Michalski JM., Park TS., Perry A., Simpson JR., Mansur DB.

Data di Pubblicazione: 2011-8-16

Abstract: Oligodendrogliomas are rare central nervous system (CNS) tumors in children. The purpose of this study was to identify prognostic factors for progression free survival (PFS) and overall survival (OS) in pediatric patients with oligodendrogliomas. We retrospectively analyzed clinical data on 37 pediatric patients with oligodendroglial tumors treated at Washington University. Kaplan-Meier method was used to calculate survival rates. Log-rank was used to detect the difference between survival curves. The median age was 11.1 years (range 10 months-18 years), and median follow-up was 4.5 years (range 2 months-30.5 years). The 5-year PFS and OS were 66.4 and 93.4%, respectively. Mixed histology was associated with worse OS compared to patients with pure oligodendroglioma, 5-year OS 77.6 versus 100% ( $P < 0.01$ ). Patients who underwent gross total resection (GTR) experienced an improved 5-year PFS of 100% compared to 28.8% ( $P = 0.03$ ) in patients treated with subtotal resection (STR) or biopsy alone. Age  $>3$  years at diagnosis correlated with improved 5-year PFS, 33.3 versus 69.8% ( $P = 0.01$ ). Neither post-operative chemotherapy nor radiation therapy correlated with improved outcome. GTR and age  $>3$  years at diagnosis remained significant for improved PFS on multivariate analysis. There were no factors correlated with improved overall survival on multivariate analysis. Pediatric oligodendroglial tumors are associated with excellent OS; however, a third of patients developed progressive disease. Our data demonstrate that patients with less than GTR and  $<3$  years at diagnosis are at increased risk for progression and may benefit from more aggressive therapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 21827415

DOI: doi.org/10.2174/138161211797249189

Titolo: The role of integrins in glioma biology and anti-glioma therapies.



Autori: Tabatabai G., Tonn JC., Stupp R., Weller M.

Data di Pubblicazione: 2011-8-11

Abstract: The tumor environment is critical for tumor maintenance and progression. Integrins are a large family of cell surface receptors mediating the interaction of tumor cells with their microenvironment and play important roles in glioma biology, including migration, invasion, angiogenesis and tumor stem cell anchorage. Here, we review preclinical and clinical data on integrin inhibition in malignant gliomas. Various pharmacological approaches to the modulation of integrin signaling have been explored including antibodies and peptide-based agents. Cilengitide, a cyclic RGD-mimetic peptide of  $\alpha v\beta 3$  and  $\alpha v\beta 5$  integrins is in advanced clinical development in glioblastoma. Cilengitide had only limited activity as a single agent in glioblastoma, but, when added to standard radiochemotherapy, appeared to prolong progression-free and overall survival in patients with newly diagnosed glioblastomas and methylation of the promoter of the O<sup>6</sup> methylguanine methyltransferase (MGMT) gene. MGMT gene promoter methylation in turn predicts benefit from alkylating chemotherapy. A phase III randomized clinical trial in conjunction with standard radiochemotherapy in newly diagnosed glioblastoma patients with MGMT gene promoter methylation has recently completed accrual (EORTC 26071-22072). A companion trial explores a dose-escalated regimen of cilengitide added to radiotherapy plus temozolomide in patients without MGMT gene promoter methylation. Promising results in these trials would probably result in a broader interest in integrins as targets for glioma therapy and hopefully the development of a broader panel of anti-integrin agents.

Journal Title: Current pharmaceutical design

PUBMED ID: 21813279

DOI: doi.org/10.1016/j.jocn.2011.02.026

Titolo: Phase 2 trial of temozolomide and pegylated liposomal doxorubicin in the treatment of patients with glioblastoma multiforme following concurrent radiotherapy and chemotherapy.

Autori: Ananda S., Nowak AK., Cher L., Dowling A., Brown C., Simes J., Rosenthal MA., Rosenthal MA.

Data di Pubblicazione: 2011-8-5

Abstract: Concurrent and post-radiotherapy temozolomide (T) significantly improves survival in patient with newly diagnosed glioblastoma multiforme. We aimed to assess the activity of the combination of T and pegylated liposomal doxorubicin (PLD) in this population. A combination of T (days 1-5, 200mg/m<sup>2</sup> orally) and PLD (day 1, 40 mg/m<sup>2</sup> intravenous) was given every 4 weeks for six cycles following chemo-radiotherapy as a post-operative treatment. The primary endpoint was 6-month progression free survival (6PFS). Of the 40 patients who enrolled (53 years median age, 73% male), the 6PFS was 58% (95% confidence interval [CI], 41-72%). The median time to progression was 6.2 months (95% CI, 5.6-8.0 months) and overall survival (OS) was 13.4 months (95% CI, 12.7-15.8 months). Thirty-four patients had measurable disease: one had a complete response (3%), 28 had stable disease (82%), and five had progressive disease (15%). Treatment was well tolerated: hematological toxicity included grade 3 neutropenia (8%). Grade 3 non-hematologic toxicity included nausea and vomiting (8%) and palmar-plantar toxicity (5%). We concluded that combination T and PLD is well tolerated but does not add significant clinical benefit regarding 6PFS and OS.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 21807073

DOI: doi.org/10.1016/j.brainresbull.2011.07.010

Titolo: Candidate genes influencing sensitivity and resistance of human glioblastoma to Semustine.

Autori: Zhao Z., Liu Y., He H., Chen X., Chen J., Lu YC.

Data di Pubblicazione: 2011-8-3

Abstract: Bioinformatics may help excavate and analyze large amounts of data in microarrays by means of rigorous experimental planning, scientific statistical analysis and collection of complete data about survival of GBM patients. In the present study, a novel differential gene expression pattern was constructed and advanced study will provide new targets for chemosensitivity of GBM.

Journal Title: Brain research bulletin

PUBMED ID: 21806354

DOI: doi.org/10.3171/2011.5.PEDS1178

Titolo: Multidisciplinary management of childhood brain tumors: a review of outcomes, recent advances, and challenges.

Autori: Pollack IF.

Data di Pubblicazione: 2011-8-3

Abstract: Advances in the clinical and molecular stratification for many types of childhood brain tumors have provided a foundation for risk-adapted treatment planning and improvements in outcome. In some instances, molecular characterization approaches have also yielded insights into new therapeutic targets. For other tumor types, outcome remains discouraging, although new information regarding the biological features critical to tumorigenesis are being translated into novel therapeutic approaches that hold promise for future improvements.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 21792866

DOI: doi.org/10.1002/cncr.26381

Titolo: Bevacizumab and daily temozolomide for recurrent glioblastoma.

Autori: Desjardins A., Reardon DA., Coan A., Marcello J., Herndon JE., Bailey L., Peters KB., Friedman HS., Vredenburgh JJ.

Data di Pubblicazione: 2011-7-28

Abstract: The current study demonstrated that a regimen of combined daily temozolomide and biweekly bevacizumab had some activity and was well tolerated. However, the results obtained in this study were inferior to those observed in studies of bevacizumab monotherapy and of combined irinotecan and bevacizumab therapy. The current patient population was more heterogeneous and was pretreated more heavily than patients in previous studies.

Journal Title: Cancer

PUBMED ID: 21764821

DOI: doi.org/10.1093/neuonc/nor090

Titolo: A phase 1 study of vinblastine in combination with carboplatin for children with low-grade gliomas: a Children's Oncology Group phase 1 consortium study.

Autori: Jakacki RI., Bouffet E., Adamson PC., Pollack IF., Ingle AM., Voss SD., Blaney SM.

Data di Pubblicazione: 2011-7-19

Abstract: Both carboplatin and vinblastine have demonstrated single-agent activity in children with low-grade gliomas. A phase 1 trial evaluating 2 different schedules of these 2 agents in combination was performed: (1) Schedule A = carboplatin (140 mg/m<sup>2</sup>) weekly × 3 + vinblastine (4.5 or 3.5 mg/m<sup>2</sup>) weekly × 6, every 6 weeks; (2) Schedule B = carboplatin (300, 400, or 500 mg/m<sup>2</sup>) on day 1 + vinblastine (4.0 mg/m<sup>2</sup>) weekly × 3, every 4 weeks. Twenty-six patients, median (range) age 4.4 (0.7-14.8) years, were enrolled. Four

of 9 patients enrolled on Schedule A had recurrent grade 4 neutropenia, suggesting that this schedule was not feasible. Seventeen patients were enrolled on Schedule B. At the 500 mg/m<sup>2</sup> carboplatin dose level, 2 of 3 patients developed dose-limiting toxicity (elevated alkaline phosphatase, neutropenia). At the 400 mg/m<sup>2</sup> carboplatin dose level, none of the 6 patients had dose-limiting toxicity. Ten of 16 patients who received treatment on Schedule B completed the prescribed 12 courses. Of the 21 patients evaluable for response, central review confirmed 1 partial response and 6 minor responses. Eleven patients had stable disease (>3 months) and 3 developed progressive disease. Seven of 9 patients with visual pathway tumors and acute visual changes prior to enrollment had documented improvement. The recommended phase 2 dose and schedule is carboplatin, 400 mg/m<sup>2</sup>/dose on day 1, and vinblastine, 4 mg/m<sup>2</sup>/dose, weekly × 3, repeated every 4 weeks. Further study of this regimen in patients with low-grade glioma is warranted.

Journal Title: Neuro-oncology

PUBMED ID: 21748491

DOI: doi.org/10.1007/s11060-011-0657-7

Titolo: Using different schedules of Temozolomide to treat low grade gliomas : systematic review of their efficacy and toxicity.

Autori: Lashkari HP., Saso S., Moreno L., Athanasiou T., Zacharoulis S.

Data di Pubblicazione: 2011-7-13

Abstract: Low grade gliomas (LGG) contribute to 50% of all central nervous tumors in children and 15% of all gliomas in adults. Temozolomide (TMZ) is an oral alkylating agent with activity in high and LGG. Various regimens of TMZ are currently in use. We attempted to assess the impact of different TMZ regimens on the treatment of LGG. A systematic review of the literature identified all the studies published in Pubmed, EMBASE and Cochrane databases which met the inclusion criteria. The primary outcome measure was the impact of different TMZ regimens on the 12 month progression-free survival (PFS) rates of patients diagnosed with progressive LGG. Secondary outcome measures looked at the ability of the three regimens to elicit an objective response and the associated toxicity. Statistical pooling and calculation of weighted mean average of each proportion (WMA) was conducted using a random-effects model. 18 studies (736 patients) were analyzed. PFS at 12 months revealed a WMA of 0.61 (95% CI 0.44-0.78) for regimen A, 0.59 (0.28-0.89) for regimen B, and 0.91 (95% CI 0.83-0.99) for regimen C (Regimen A--200 mg/m<sup>2</sup>/day for 5 days, repeated every 4 weeks; B--75 mg/m<sup>2</sup>/day for 21 days repeated every 4 weeks; C--75 mg/m<sup>2</sup>/day for 7 weeks with 4 weeks of every 11 weeks). In terms of objective response, WMA were 0.19 (95% CI 0.13-0.25), 0.27 (95% CI 0.15-0.39) and 0.21 (95% CI 0.10-0.32) for regimen A, B, C respectively. When analyzing hematological toxicity, WMAs were 0.14 (95% CI 0.11-0.18), 0.35 (0.14-0.56) and 0.23 (95% CI 0.03-0.43). The bulk of evidence originates from the standard 5 day/month regimen A but with a lack of comparative studies. Analysis revealed significant heterogeneity. Although there is possibly an indication that metronomic regimens of TMZ result in better PFS and response rate when compared to the conventional standard 5 day regimen, insufficient available data and study heterogeneity preclude any safe conclusions. Well designed randomized controlled clinical trials are needed to establish the efficacy of metronomic regimens of TMZ in LGGs.

Journal Title: Journal of neuro-oncology

PUBMED ID: 21740923

DOI: doi.org/10.1016/j.pbiomolbio.2011.06.007

Titolo: Coupling biomechanics to a cellular level model: an approach to patient-specific image driven multi-scale and multi-physics tumor simulation.

Autori: May CP., Kolokotroni E., Stamatakis GS., Büchler P.

Data di Pubblicazione: 2011-7-12

**Abstract:** Modeling of tumor growth has been performed according to various approaches addressing different biocomplexity levels and spatiotemporal scales. Mathematical treatments range from partial differential equation based diffusion models to rule-based cellular level simulators, aiming at both improving our quantitative understanding of the underlying biological processes and, in the mid- and long term, constructing reliable multi-scale predictive platforms to support patient-individualized treatment planning and optimization. The aim of this paper is to establish a multi-scale and multi-physics approach to tumor modeling taking into account both the cellular and the macroscopic mechanical level. Therefore, an already developed biomodel of clinical tumor growth and response to treatment is self-consistently coupled with a biomechanical model. Results are presented for the free growth case of the imageable component of an initially point-like glioblastoma multiforme tumor. The composite model leads to significant tumor shape corrections that are achieved through the utilization of environmental pressure information and the application of biomechanical principles. Using the ratio of smallest to largest moment of inertia of the tumor material to quantify the effect of our coupled approach, we have found a tumor shape correction of 20% by coupling biomechanics to the cellular simulator as compared to a cellular simulation without preferred growth directions. We conclude that the integration of the two models provides additional morphological insight into realistic tumor growth behavior. Therefore, it might be used for the development of an advanced oncosimulator focusing on tumor types for which morphology plays an important role in surgical and/or radio-therapeutic treatment planning.

**Journal Title:** Progress in biophysics and molecular biology

PUBMED ID: 21715567

DOI: doi.org/10.1158/1078-0432.CCR-10-3124

**Titolo:** Regression of glioma in rat models by intranasal application of parvovirus h-1.

**Autori:** Kiprianova I., Thomas N., Ayache A., Fischer M., Leuchs B., Klein M., Rommelaere J., Schlehofer JR.

**Data di Pubblicazione:** 2011-7-1

**Abstract:** In view of an ongoing clinical trial on the use of H-1PV for oncolytic virotherapy of glioma, the option of applying the virus intranasally may be a valuable alternative to invasive routes of infection.

**Journal Title:** Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 21715171

DOI: doi.org/10.1016/j.jocn.2010.11.034

**Titolo:** A phase I/II clinical trial investigating the adverse and therapeutic effects of a postoperative autologous dendritic cell tumor vaccine in patients with malignant glioma.

**Autori:** Chang CN., Huang YC., Yang DM., Kikuta K., Wei KJ., Kubota T., Yang WK.

**Data di Pubblicazione:** 2011-7-1

**Abstract:** Previous clinical trials of dendritic cell (DC)-based immunotherapy in patients with glioblastoma multiforme (GBM) have reported induction of systemic immune responses and prolonged survival. From 2003 to 2005, we performed a clinical trial in which patients with malignant glioma underwent surgery for maximal cytoreduction followed by a 6-month 10-injection course of autologous DC-tumor vaccine therapy, each injection containing  $1-6 \times 10^7$  DC. Of the 17 treated patients (16 with World Health Organization grade IV and one with grade III glioma), eight (47.1%) had an initial transient elevation in aspartate aminotransferase (AST)/alanine aminotransferase (ALT). Vaccination caused some tumor shrinkage and increased concentration of tumor-infiltrating CD8(+) lymphocytes. Median survival and 5-year survival were 525 days

and 18.8%, respectively, for 16 patients with grade IV glioma (381 days and 12.5% for eight newly diagnosed; 966 days and 25% for eight relapsed patients) compared to 380 days and 0% for 63 historical control patients. We concluded that autologous DC-tumor immunotherapy benefits patients with malignant glioma but may cause transient but reversible elevation of serum AST/ALT levels.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 21712019

DOI: Mancante

Titolo: Stem cell-mediated gene therapies for malignant gliomas: a promising targeted therapeutic approach?

Autori: Tabatabai G., Wick W., Weller M.

Data di Pubblicazione: 2011-6-30

Abstract: Glioblastomas are aggressive intrinsic brain tumors. The median overall survival does not exceed 15 months despite surgical resection, radiotherapy, and chemotherapy even in selected clinical trial populations. One reason for this poor outcome is the characteristic infiltrative growth pattern of glioblastomas with tumor cells deeply infiltrating into the normal brain parenchyma and thereby escaping surgical debulking and involved-field radiation therapy. Novel therapeutic strategies are urgently needed including those that target disseminated tumor cells, too. In this regard, the application of adult stem cells as cellular vehicles for the delivery of therapeutic molecules has emerged during the last decade as an experimental approach. Adult stem cells with a tropism for gliomas include neural stem and progenitor cells, mesenchymal stem cells, hematopoietic progenitor cells, and endothelial progenitor cells. Importantly, these candidate cellular carriers also localize to sites of hypoxia and invasive tumor borders which are usually not targeted by currently available therapeutic approaches. Stem cell-based therapeutic approaches could therefore help to overcome some of the current limitations of radio- and chemotherapy and may circumvent toxicity to normal resident cells of the central nervous system. The development of neural stem- and progenitor-based therapies is advanced with a currently ongoing phase I clinical study. We review rationale, achievements, and future challenges in this field.

Journal Title: Discovery medicine

PUBMED ID: 21707241

DOI: doi.org/10.3109/02688697.2011.583365

Titolo: Differential expression of a novel voltage gated potassium channel--Kv 1.5 in astrocytomas and its impact on prognosis in glioblastoma.

Autori: Arvind S., Arivazhagan A., Santosh V., Chandramouli BA.

Data di Pubblicazione: 2011-6-29

Abstract: Kv1.5 expression occurs more in DA, when compared to high grade astrocytoma. GBM patients with higher Kv1.5 expression had better survival, though not reaching statistical significance.

Journal Title: British journal of neurosurgery

PUBMED ID: 21699466

DOI: doi.org/10.3109/08880018.2011.563774

Titolo: Potential role for valproate in the treatment of high-risk brain tumors of childhood--results from a retrospective observational cohort study.

Autori: Felix FH., Trompieri NM., de Araujo OL., da Trindade KM., Fontenele JB.

Data di Pubblicazione: 2011-6-25

**Abstract:** Although substantial progress has been made in pediatric brain tumor management, patients with brainstem tumors and high-grade gliomas, as well as patients less than 3 years of age with high-risk malignant tumors, have a poorer prognosis. The authors have been treating these patients with radiotherapy and standard carboplatin and vincristine chemotherapy. Since January 2007 the authors have been using valproate as anticonvulsant for prophylaxis. The authors performed a retrospective cohort analysis of pediatric patients with high-risk brain tumors treated with chemotherapy, radiotherapy, and valproate prophylaxis, comparing this group with a historical control. The 2007-2008 group was comprised of 22 patients, 15 with brainstem tumors (7 diffuse intrinsic pontine glioma [DIPG], 3 focal, the remaining infiltrating with a solid portion), 4 with diencephalic tumors (2 thalamic), and 3 with supratentorial high-grade tumors (1 glioblastoma, 1 recurrent grade III ependymoma, 1 with gliomatosis). There were 15 patients alive (68%) after a mean follow-up time of 19 months. Survival function comparison by log rank test was highly significant ( $P = .004$ ) with a hazard ratio of 0.31 (0.14-0.70). Radiological response showed 3 complete responses (14%), 8 partial responses (36%), 5 stable diseases (23%), and 5 progressive diseases (23%). The authors hypothesize that valproate may have potentiated the antiangiogenic effect of vincristine, diminished expression of resistance to carboplatin, and sensitized tumor cells to radiotherapy. The authors suggest that clinical trials of carboplatin and vincristine associated with oral continuous low-dose valproate are indicated for pediatric patients with high-risk brain tumor.

**Journal Title:** Pediatric hematology and oncology

PUBMED ID: 21636712

DOI: doi.org/10.1093/neuonc/nor045

**Titolo:** Thalamic high-grade gliomas in children: a distinct clinical subset?

**Autori:** Kramm CM., Butenhoff S., Rausche U., Warmuth-Metz M., Kortmann RD., Pietsch T., Gnekow A., Jorch N., Janssen G., Berthold F., Wolff JE.

**Data di Pubblicazione:** 2011-6-4

**Abstract:** Pediatric high-grade gliomas (HGGs) of the thalamic region account for up to 13% of pediatric HGGs and usually result in only anecdotal long-term survival. Because very little is known about these tumors, we aimed to further characterize them. In our series of 99 pediatric thalamic HGGs, there were no significant differences in survival between patients with tumors affecting the thalamus alone (including bithalamic lesions) and patients with tumors affecting the thalamus plus adjacent structures. Tumor resection (event-free survival/overall survival) and an early treatment response to radiotherapy/chemotherapy (event-free survival) had independent prognostic significance, as shown by Kaplan-Meier and multivariate Cox regression analyses. When we compared clinical characteristics and outcomes of pediatric thalamic HGG with those of pediatric (nonthalamic) supratentorial ( $n = 177$ ) as well as pediatric pontine HGG (including diffuse intrinsic pontine gliomas;  $n = 234$ ), we found that thalamic HGG shared more similarities with pontine than with supratentorial HGG, but overall, it appeared to represent a clinically distinct subgroup of pediatric HGG. The varying extent of tumor resection in the different tumor localizations may play some role in the observed clinical differences, as shown by multivariate Cox regression analyses, but the tumor site itself was also identified as an independent prognostic parameter. Thus, an additional location-specific effect on survival and/or tumor biology, despite different neurosurgical accessibility, has to be considered. Therefore, future investigations should try to further characterize the obviously site-specific heterogeneity of pediatric HGG on a molecular genetic basis.

**Journal Title:** Neuro-oncology

PUBMED ID: 21610707

DOI: doi.org/10.1038/bjc.2011.174

Titolo: Predicting the outcome of grade II glioma treated with temozolomide using proton magnetic resonance spectroscopy.  
Autori: Guillemin R., Menuel C., Taillibert S., Capelle L., Costalat R., Abud L., Habas C., De Marco G., Hoang-Xuan K., Chiras J., Vallée JN.  
Data di Pubblicazione: 2011-5-26  
Abstract: The (1)H-MRS profile changes more widely and rapidly than tumour volume during the response and relapse phases, and represents an early predictive factor of outcome over 14 months of follow-up. Thus, (1)H-MRS may be a promising, non-invasive tool for predicting and monitoring the clinical response to TMZ.  
Journal Title: British journal of cancer

PUBMED ID: 21590996  
DOI: doi.org/10.1002/jmri.22563  
Titolo: Detection of early response to temozolomide treatment in brain tumors using hyperpolarized <sup>13</sup>C MR metabolic imaging.  
Autori: Park I., Bok R., Ozawa T., Phillips JJ., James CD., Vigneron DB., Ronen SM., Nelson SJ.  
Data di Pubblicazione: 2011-5-19  
Abstract: The results from this study suggest that metabolic imaging with hyperpolarized [1-(<sup>13</sup>C)]-pyruvate may provide a unique tool that clinical neuro-oncologists can use in the future to monitor tumor response to therapy for patients with brain tumors.  
Journal Title: Journal of magnetic resonance imaging : JMRI

PUBMED ID: 21590689  
DOI: doi.org/10.1002/cncr.26188  
Titolo: Phase 2 study of carboplatin, irinotecan, and bevacizumab for recurrent glioblastoma after progression on bevacizumab therapy.  
Autori: Reardon DA., Desjardins A., Peters KB., Vredenburgh JJ., Gururangan S., Sampson JH., McLendon RE., Herndon JE., Coan A., Threatt S., Friedman AH., Friedman HS.  
Data di Pubblicazione: 2011-5-19  
Abstract: Carboplatin, irinotecan, and bevacizumab was associated with modest activity and adequate safety among recurrent GBM patients who progressed on bevacizumab previously.  
Journal Title: Cancer

PUBMED ID: 21567301  
DOI: doi.org/10.1007/s11060-011-0601-x  
Titolo: Proton magnetic resonance spectroscopy predicts survival in children with diffuse intrinsic pontine glioma.  
Autori: Steffen-Smith EA., Shih JH., Hipp SJ., Bent R., Warren KE.  
Data di Pubblicazione: 2011-5-14  
Abstract: Patients with diffuse intrinsic pontine glioma (DIPG) face a grim prognosis with limited treatment options. Many patients will enroll on investigational trials though the role of chemotherapy or immunotherapy is unclear. Radiographic changes on conventional MRI are used to evaluate tumor response and progression, but are not predictive of outcome in these patients. More sensitive measures of tumor biology are needed to improve patient management. We evaluated changes in magnetic resonance spectroscopy (MRS) biomarkers in patients with DIPG. Thirty-eight patients were enrolled prospectively on an IRB-approved protocol, which included standard MRI, single voxel spectroscopy (SVS) and multi-slice multi-voxel spectroscopy (MRSI). Scans were performed at multiple time points during each patient's clinical course, with a total of 142 scans. The prognostic values of Choline:N-acetylaspartate (Cho:NAA), Cho:Creatine (Cho:Cr) and the presence of lactate and lipids (+Lac/Lip

) were evaluated. Cho:NAA and variance in Cho:NAA values among different voxels within a tumor were each predictive of shorter survival. This prospective study shows that MRS can be used to identify high-risk patients and monitor changes in tumor metabolism, which may reflect changes in tumor behavior.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 21558404

DOI: doi.org/10.1158/1078-0432.CCR-10-3194

Titolo: Molecular markers in low-grade gliomas: predictive or prognostic?

Autori: Hartmann C., Hentschel B., Tatagiba M., Schramm J., Schnell O., Seidel C., Stein R., Reifenberger G., Pietsch T., von Deimling A., Loeffler M., Weller M., Weller M.

Data di Pubblicazione: 2011-5-12

Abstract: None of the parameters are sensitive prognostic biomarkers in WHO grade II glioma patients who do not receive radiotherapy or chemotherapy after surgery. Limitations of this study include the selection of patients with favorable outcome, the nonrandomized allocation of treatment, and the insufficient sample size to distinguish between effects of radiotherapy versus chemotherapy. Regardless of histology, IDH1 mutation status is the strongest prognostic marker for OS.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 21558074

DOI: doi.org/10.1093/neuonc/nor024

Titolo: Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab.

Autori: Wefel JS., Cloughesy T., Zazzali JL., Zheng M., Prados M., Wen PY., Mikkelsen T., Schiff D., Abrey LE., Yung WK., Paleologos N., Nicholas MK., Jensen R., Vredenburgh J., Das A., Friedman HS.

Data di Pubblicazione: 2011-5-12

Abstract: Neurocognitive decline is a frequent adverse effect of glioblastoma. Antitumor therapies that are efficacious, as measured by traditional endpoints such as objective response (OR) and progression-free survival (PFS), and have beneficial effects on neurocognitive function (NCF) are of clinical benefit to these patients. We evaluated neurocognitive changes across time in 167 patients with recurrent glioblastoma treated with bevacizumab-based therapy in BRAIN, a phase II, randomized, multicenter trial. All patients underwent MRI and neurocognitive testing at baseline and every 6 weeks thereafter. Memory, visuomotor scanning speed, and executive function were evaluated using the Hopkins Verbal Learning Test-Revised, the Trail Making Test, and the Controlled Oral Word Association test, respectively. NCF relative to baseline for patients with an OR, PFS >6 months, or disease progression was evaluated at time of OR, 24 weeks, and time of progression, respectively. For patients with an OR or PFS >6 months, median standardized test scores were examined from baseline to week 24. Most patients with an OR or PFS >6 months had poorer NCF performance compared to the general population at baseline and had improved or stable NCF at the time of response or at the 24-week assessment, respectively; most patients with progressive disease had neurocognitive decline at the time of progression. For patients with an OR or PFS >6 months, median standardized test scores were largely stable across the first 24 weeks on study. Neurocognitive testing was an objective, valid, and feasible method of monitoring NCF in patients with recurrent glioblastoma.

Journal Title: Neuro-oncology

PUBMED ID: 21557457

DOI: doi.org/10.1002/pbc.22917



Titolo: Feasibility and efficacy of repeated chemotherapy for progressive pediatric low-grade gliomas.

Autori: Scheinemann K., Bartels U., Tsangaris E., Hawkins C., Huang A., Dirks P., Fried I., Bouffet E., Tabori U.

Data di Pubblicazione: 2011-5-11

Abstract: This study demonstrates high feasibility and low mortality of repeated chemotherapy treatment for progressive LGG. The chronic nature of LGG concerning tumor progression justifies consideration of non-toxic second-line treatment regimens at the time of recurrence. Prospective studies focusing on toxicity and long-term outcome are needed to substantiate this approach.

Journal Title: Pediatric blood & cancer

PUBMED ID: 21538632

DOI: doi.org/10.1002/nbm.1669

Titolo: Assessment of therapeutic response and treatment planning for brain tumors using metabolic and physiological MRI.

Autori: Nelson SJ.

Data di Pubblicazione: 2011-5-4

Abstract: MRI is routinely used for diagnosis, treatment planning and assessment of response to therapy for patients with glioma. Gliomas are spatially heterogeneous and infiltrative lesions that are quite variable in terms of their response to therapy. Patients classified as having low-grade histology have a median overall survival of 7 years or more, but need to be monitored carefully to make sure that their tumor does not upgrade to a more malignant phenotype. Patients with the most aggressive grade IV histology have a median overall survival of 12-15 months and often undergo multiple surgeries and adjuvant therapies in an attempt to control their disease. Despite improvements in the spatial resolution and sensitivity of anatomic images, there remain considerable ambiguities in the interpretation of changes in the size of the gadolinium-enhancing lesion on T(1) -weighted images as a measure of treatment response, and in differentiating between treatment effects and infiltrating tumor within the larger T(2) lesion. The planning of focal therapies, such as surgery, radiation and targeted drug delivery, as well as a more reliable assessment of the response to therapy, would benefit considerably from the integration of metabolic and physiological imaging techniques into routine clinical MR examinations. Advanced methods that have been shown to provide valuable data for patients with glioma are diffusion, perfusion and spectroscopic imaging. Multiparametric examinations that include the acquisition of such data are able to assess tumor cellularity, hypoxia, disruption of normal tissue architecture, changes in vascular density and vessel permeability, in addition to the standard measures of changes in the volume of enhancing and nonenhancing anatomic lesions. This is particularly critical for the interpretation of the results of Phase I and Phase II clinical trials of novel therapies, which are increasingly including agents that are designed to have anti-angiogenic and anti-proliferative properties as opposed to having a direct effect on tumor cell viability.

Journal Title: NMR in biomedicine

PUBMED ID: 21531084

DOI: doi.org/10.1016/j.prp.2011.03.002

Titolo: Epidermal growth factor receptor (EGFR) and squamous cell carcinoma of the skin: molecular bases for EGFR-targeted therapy.

Autori: Uribe P., Gonzalez S.

Data di Pubblicazione: 2011-5-3

Abstract: Cutaneous squamous cell carcinoma (SCC) ranks second in the frequency of all skin tumors. Its incidence has risen significantly due to an increased sun exposure and the number of immunocompromised patients. It has a well-defined progression with known precursor lesions called actinic keratosis

. The degree of cellular differentiation, tumor thickness, location, and other features has prognostic value. It has a better prognosis than mucosal SCC of the head and neck, also called head and neck squamous cell carcinoma (HNSCC). Ultraviolet light plays a fundamental role as an initiator and promoter of carcinogenesis of SCC, allowing the accumulation of genetic alterations that allows a selective growth advantage. The TP53 (p53) gene often mutates and Ras is frequently activated, but with low frequency of mutations. Normally, the extracellular signals determine whether the cells move from a quiescent state into an active proliferative state. In tumor cells an increase in the production of growth factors and its receptors can be often seen that gives rise to such an autocrine circuit facilitating cellular division. Recently, frequent mutations in the epidermal growth factor receptor (EGFR) have been detected in lung cancer, mainly deletions in exon 19 and L858R mutation in exon 21. These are located at the EGFR tyrosine kinase domain (TK). EGFR TK mutations produce activation of the signaling pathways downstream and preferentially activated antiapoptotic pathways (PI3K/AKT, JAK-STAT and ERK/MAPK). These mutations are correlated with the clinical response of patients to tyrosine kinase inhibitors (gefitinib and erlotinib), because the tumor cells are addicted to the constant activation of specific signaling pathways. Glioblastoma shows another EGFR mutation (EGFRvIII), corresponding to a deletion of the extracellular domain, and it is present in 24-67% of these tumors. This variant has been found in 42% of HNSCC, related to the poor response to monoclonal antibody cetuximab. Many observations show that there are abnormalities in the expression of epidermal growth factor receptor (EGFR) and/or its ligands in HNSCC with frequent activation of multiple pathways downstream EGFR, and unrelated to RAS mutation. This suggests the possibility of activation by mutation or overexpression of a component of the pathway located upstream-Ras. While in other tumors, especially lung cancer and glioblastoma, the EGFR mutations are frequent genetic events, it is unknown whether EGFR is mutated or amplified in SCC of the skin and what would be its pathogenic role in this malignancy and its precursors.

Journal Title: Pathology, research and practice

PUBMED ID: 21515959

DOI: doi.org/10.2176/nmc.51.319

Titolo: Pathological changes after autologous formalin-fixed tumor vaccine therapy combined with temozolomide for glioblastoma - three case reports - .

Autori: Sakamoto N., Ishikawa E., Yamamoto T., Satomi K., Nakai K., Sato M., Enomoto T., Morishita Y., Takano S., Ohno T., Tsuboi K., Matsumura A.

Data di Pubblicazione: 2011-4-26

Abstract: Temozolomide (TMZ), an alkylating agent widely used for patients with glioblastoma multiforme (GBM), has the potential to enhance the acquired immune response to GBM. Here, we describe 3 cases of GBM patients treated with autologous formalin-fixed tumor vaccine (AFTV) combined with TMZ. All cases demonstrated pathological changes associated with the therapy. After a 4-week break from the standard initial treatments, 1 patient with primary GBM and 2 patients with secondary GBM received adjuvant TMZ for 5 days combined with AFTV injection and were subsequently treated with multiple cycles of adjuvant TMZ for 5 days every 28 days (AFTV/TMZ therapy). Adverse effects related to AFTV plus TMZ were very minor in all patients. Magnetic resonance imaging revealed partial response in 2 patients. CD3(+)CD8(+) lymphocytes were frequently detected in surgical specimens and MIB-1 labeling index in 2 cases decreased after AFTV/TMZ therapy. AFTV/TMZ therapy is suitable for larger scale clinical trials.

Journal Title: Neurologia medico-chirurgica

PUBMED ID: 21515957

DOI: doi.org/10.2176/nmc.51.310

Titolo: Pleomorphic xanthoastrocytoma and moyamoya disease in a patient with neurofibromatosis type 1 - case report - .

Autori: Horiguchi S., Mitsuya K., Watanabe R., Yagishita S., Nakasu Y.

Data di Pubblicazione: 2011-4-26

Abstract: A 32-year-old man with familial neurofibromatosis type 1 presented with a rare case of coexisting pleomorphic xanthoastrocytoma (PXA) and moyamoya disease manifesting as progressive right hemiparesis. Magnetic resonance (MR) imaging with gadolinium showed an enhanced mass lesion in the left basal ganglia extending to the left parietal lobe. Preoperative angiography showed severe stenosis of the bilateral internal carotid arteries, and moyamoya vessels. The patient underwent open biopsy. Histological examination showed the characteristic findings of PXA. After radiation therapy and chemotherapy, MR imaging showed decreased size and enhancement of the tumor, but his clinical condition worsened with generalized convulsions and consciousness disturbance. He died 1 year and 6 months after the first presentation. Autopsy findings demonstrated necrosis in the main mass and tumor cell dissemination without anaplastic change. The rare combination of PXA and moyamoya disease in the basal ganglia limited treatment options. Injured moyamoya vessels and ischemic condition might have caused tumor progression and dissemination. Radiation therapy, in combination with moyamoya disease, induced decreased cerebral blood flow (CBF) in the left frontal lobe. Tumor dissemination, CBF decrease, and hydrocephalus led to the clinical deterioration of this patient. Journal Title: Neurologia medico-chirurgica

PUBMED ID: 21499132

DOI: doi.org/10.1097/CJI.0b013e318215e300

Titolo: Immune response in patients with newly diagnosed glioblastoma multiforme treated with intranodal autologous tumor lysate-dendritic cell vaccination after radiation chemotherapy.

Autori: Fadul CE., Fisher JL., Hampton TH., Lallana EC., Li Z., Gui J., Szczepiorkowski ZM., Tosteson TD., Rhodes CH., Wishart HA., Lewis LD., Ernstoff MS.

Data di Pubblicazione: 2011-4-19

Abstract: Patients with glioblastoma multiforme (GBM) are profoundly immunosuppressed and may benefit from restoration of an antitumor immune response in combination with conventional radiation therapy and temozolomide (TMZ). The optimal strategies to evaluate clinically relevant immune responses to treatment have yet to be determined. The primary objective of our study was to determine immunologic response to cervical intranodal vaccination with autologous tumor lysate-loaded dendritic cells (DCs) in patients with GBM after radiation therapy and TMZ. We used a novel hierarchical clustering analysis of immune parameters measured before and after vaccination. Secondary objectives were to assess treatment feasibility and to correlate immune response with progression-free survival (PFS) and overall survival. Ten eligible patients received vaccination. Tumor-specific cytotoxic T-cell response measured after vaccination was enhanced for the precursor frequency of CD4+ T and CD4+ interferon  $\gamma$ -producing cells. Hierarchical clustering analysis of multiple functional outcomes discerned 2 groups of patients according to their immune response, and additionally showed that patients in the top quintile for at least one immune function parameter had improved survival. There were no serious adverse events related to DC vaccination. All patients were alive at 6 months after diagnosis and the 6-month PFS was 90%. The median PFS was 9.5 months and overall survival was 28 months. In patients with GBM, immune therapy with DC vaccination after radiation and TMZ resulted in tumor-specific immune responses that were associated with prolonged survival. Our data suggest that DC vaccination in combination with radiation and chemotherapy in patients with GBM is feasible, safe, and may induce tumor-specific immune responses.

Journal Title: Journal of immunotherapy (Hagerstown, Md. : 1997)

PUBMED ID: 21489708

DOI: doi.org/10.1016/j.ijrobp.2010.12.074

Titolo: Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas.

Autori: Cuneo KC., Vredenburgh JJ., Sampson JH., Reardon DA., Desjardins A., Peters KB., Friedman HS., Willett CG., Kirkpatrick JP.

Data di Pubblicazione: 2011-4-15

Abstract: The combination of salvage radiosurgery and bevacizumab to treat recurrent malignant gliomas is well tolerated and seems to be associated with improved outcomes. Prospective multiinstitutional studies are required to determine efficacy and long-term toxicity with this approach.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 21474302

DOI: doi.org/10.1016/j.ejca.2011.03.004

Titolo: Treatment of recurrent central nervous system primitive neuroectodermal tumours in children and adolescents: results of a Children's Cancer and Leukaemia Group study.

Autori: Pizer B., Donachie PH., Robinson K., Taylor RE., Michalski A., Punt J., Ellison DW., Picton S.

Data di Pubblicazione: 2011-4-9

Abstract: This national study based on a strategy including a particular tandem HDCT regimen showed no benefit for previously irradiated patients with relapsed StPNET and very limited benefit for patients with relapsed medulloblastoma.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 21456916

DOI: doi.org/10.3171/2011.1.PEDS10258

Titolo: Diffuse hemispheric dysembryoplastic neuroepithelial tumor: a new radiological variant associated with early-onset severe epilepsy.

Autori: Bird-Lieberman G., Sethi K., Childs AM., Chumas P., Crimmins D., Ismail A., Livingston J.

Data di Pubblicazione: 2011-4-5

Abstract: The authors describe the clinical and radiological features in 3 children with a diffuse hemispheric dysembryoplastic neuroepithelial tumor (DNET) presenting with severe epilepsy and a previously unreported and characteristic MR imaging appearance. The DNET is a well-recognized cause of focal epilepsy, usually with a very good response to resection. These tumors are usually intracortical, and most commonly arise in the temporal lobe or frontal lobes. Radiologically they are usually sharply demarcated, and show little contrast enhancement. Three children (2 boys and 1 girl) presented at 14, 17, and 22 months of age with epileptic seizures. The seizures were focal motor or complex focal. One patient had epileptic spasms. The response to antiepileptic drug therapy was poor. Motor and cognitive development was delayed in all patients. One patient developed a severe epileptic encephalopathy, with regression of motor and cognitive skills. Her electroencephalogram obtained at that time showed hypsarhythmia. Admission MR imaging showed a diffuse unilateral abnormality involving frontal, temporal, and parietal lobes with little or no mass effect. There was involvement of both gray and white matter, with a striking sparing of the internal capsule in spite of apparent tumor throughout the basal ganglia and thalamus. In 2 patients there was prominent expansion of cortical gyri by tumor. In 1 child the initial radiological diagnosis was a middle cerebral artery infarct. On subsequent review the radiological diagnosis was thought to be low-grade glioma in all patients. The first patient underwent 2 limited resections involving the temporal lobe. He ha

s continued to have poorly controlled seizures and severe behavioral and cognitive problems. The other patients had subtotal resection to the level of the internal capsule. One patient is currently seizure free 24 months postsurgery, but remains cognitively impaired. The patient in Case 3 is having some seizures 3.5 years postsurgery and remains hemiplegic, but the regression has reversed and she is making steady developmental progress. The pathological specimens showed the typical features of a DNET in all cases. This striking radiological pattern has not previously been described as a feature of a DNET. Recognition of this radiological pattern in young children with epilepsy will allow early consideration for resection, which may lead to improved long-term cognitive outcome.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 21444653

DOI: doi.org/10.1177/1545968310397201

Titolo: Topical nerve growth factor as a visual rescue strategy in pediatric optic gliomas: a pilot study including electrophysiology.

Autori: Falsini B., Chiaretti A., Barone G., Piccardi M., Pierri F., Colosimo C., Lazzareschi I., Ruggiero A., Parisi V., Fadda A., Balestrazzi E., Riccardi R.

Data di Pubblicazione: 2011-3-30

Abstract: The findings from the study show that NGF administration may be an effective and safe adjunct therapy in children with optic atrophy due to OGD. The beneficial effect on optic nerve function suggests a visual rescuing mechanism exerted by murine NGF on the residual viable optic pathways.

Journal Title: Neurorehabilitation and neural repair

PUBMED ID: 21432029

DOI: doi.org/10.1007/s12325-011-0007-3

Titolo: AVAglio: Phase 3 trial of bevacizumab plus temozolomide and radiotherapy in newly diagnosed glioblastoma multiforme.

Autori: Chinot O.L., de La Motte Rouge T., Moore N., Zeaiter A., Das A., Phillips H., Modrusan Z., Cloughesy T.

Data di Pubblicazione: 2011-3-25

Abstract: Despite treatment with the current standard-of-care therapies, patients with newly diagnosed glioblastoma multiforme (GBM) exhibit dismal prognoses. Bevacizumab has demonstrated activity in patients with recurrent GBM and phase 2 trials indicate that the combination of bevacizumab with standard-of-care therapy is feasible and active for patients with newly diagnosed GBM. Bevacizumab has been granted US approval for use as single-agent therapy for patients with progressive GBM following prior therapy, although it has not received approval for use in patients with GBM in Europe. Phase 3 studies have been initiated in patients with newly diagnosed GBM and are currently recruiting patients. We describe the protocol for the AVAglio phase 3 registration trial, which is designed to evaluate the efficacy and safety of combining bevacizumab with standard-of-care therapy in patients with newly diagnosed GBM.

Journal Title: Advances in therapy

PUBMED ID: 21427185

DOI: doi.org/10.1259/bjr/29022270

Titolo: Prognostic factors in glioblastoma multiforme patients receiving high-dose particle radiotherapy or conventional radiotherapy.

Autori: Matsuda M., Yamamoto T., Ishikawa E., Nakai K., Zaboronok A., Takano S., Matsumura A.

Data di Pubblicazione: 2011-3-24

**Abstract:** The aim of this study was to evaluate the influence of prognostic factors related to patient selection on survival outcomes. Survival outcomes were retrospectively analysed in a consecutive series of 67 newly diagnosed glioblastoma multiforme (GBM) patients who had received either conventional fractionated photon radiotherapy (CRT) or high-dose particle radiotherapy (HDT). In the CRT protocol, a total dose of 60.0-61.2 Gy was administered. In the HDT protocol, an average dose of approximately 30 GyE in a single session and additional fractionated photon irradiation of total dose 30 Gy were administered to patients receiving boron neutron capture therapy; and a total dose of 96.6 GyE was administered to patients receiving proton therapy. Most of the patients had received chemotherapy with nimustine hydrochloride (ACNU) alone or with ACNU, procarbazine and vincristine. The median overall survival (OS) and progression-free survival times for all patients were 17.7 months [95% confidence interval (CI), 14.6-20.9 months] and 7.8 months (95% CI, 5.7-9.9 months), respectively. The 1- and 2-year survival rates were 67.2% and 33.7%, respectively. For patients treated with HDT, the median OS was 24.4 months (95% CI, 18.2-30.5 months), compared with 14.2 months (95% CI, 10.0-18.3 months) for those treated with CRT. The Cox proportional hazards model revealed radiation modality (HDT vs CRT) and European Organisation for Research and Treatment of Cancer recursive partitioning analysis class to be the significant prognostic factors. Age, sex, pre-operative performance status, treatment with or without advanced neuroimaging, extent of surgery and regimen of chemotherapy were not statistically significant factors in predicting prognosis. The median OS was 18.5 months (95% CI, 9.9-27.1 months) in patients of 65 years and older, compared with 16.8 months (95% CI, 13.6-20.1 months) in those 64 years and younger ( $p=0.871$ ). The positive effect of HDT treatment is unlikely to reflect patient selection alone. Randomised trials with strictly controlled inclusion criteria to ensure the comparable selection of patients are required to demonstrate conclusively that prolonged survival can be attributed to high-dose particle radiotherapies.

**Journal Title:** The British journal of radiology

PUBMED ID: 21421463

DOI: doi.org/10.1007/s12094-011-0638-5

**Titolo:** Spinal cord astrocytoma: multidisciplinary experience.

**Autori:** Tovar Martín MI., López Ramírez E., Saura Rojas E., Arregui Castillo G., Zurita Herrera M.

**Data di Pubblicazione:** 2011-3-23

**Abstract:** The optimal treatment remains controversial. Radiotherapy should be considered for tumors with high-grade histopathology, clinically progressive and when a substantial resection cannot be achieved. New therapeutic strategies need to be studied to improve survival.

**Journal Title:** Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico

PUBMED ID: 21345842

DOI: doi.org/10.1093/neuonc/noq205

**Titolo:** Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children's Oncology Group.

**Autori:** Cohen KJ., Heideman RL., Zhou T., Holmes EJ., Lavey RS., Bouffet E., Pollack IF.

**Data di Pubblicazione:** 2011-2-25

**Abstract:** An open-label phase II study (ACNS0126) testing the efficacy of chemoradiotherapy with temozolomide (TMZ) followed by adjuvant TMZ was conducted by the Children's Oncology Group. During the period from July 6, 2004 through September 6, 2005, 63 children with newly diagnosed diffuse intrinsic pontine glioma (DIPG) were enrolled in the study. All patients received TMZ a

t a dosage of 90 mg/m<sup>2</sup>/day for 42 days to a dose of 59.4 Gy. Four weeks following irradiation, TMZ was given at a dosage of 200 mg/m<sup>2</sup>/day for 5 days every 28 days, for a total of 10 cycles. The primary objective of the statistical analysis was to determine whether the current treatment produced a 1-year event-free survival (EFS) rate higher than the historical baseline of 21.9% observed in CCG-9941. The mean 1-year EFS ( $\pm$  standard deviation) was 14%  $\pm$  4.5%, compared with 21.9%  $\pm$  5% for CCG-9941. The P value of the test of comparison of 1-year EFS, based on a 1-sided, 1-sample test of proportions, was .96. There was no evidence that temozolomide produced a 1-year EFS rate higher than 21.9%. The mean 1-year OS ( $\pm$  standard deviation) was 40%  $\pm$  6.5%, compared with 32%  $\pm$  6% for CCG-9941. The median time to death was 9.6 months. Chemoradiotherapy with TMZ followed by adjuvant TMZ is not more effective than previously reported regimens for the treatment of children with DIPG.

Journal Title: Neuro-oncology

PUBMED ID: 21342033

DOI: doi.org/10.1586/era.10.227

Titolo: 2010 Society for Neuro-Oncology Annual Meeting: a report of selected studies.

Autori: Ahluwalia MS.

Data di Pubblicazione: 2011-2-24

Abstract: A number of important studies were presented at the Society for Neuro-Oncology annual meeting in Montréal, Canada, on 18-21 November 2010. Cediranib as monotherapy or in combination with lomustine did not show increased efficacy when compared with lomustine alone in patients with recurrent glioblastoma (GBM). Addition of temozolomide (TMZ) or irinotecan (CPT) to bevacizumab (BEV) in patients with recurrent GBM was well tolerated, with similar efficacy to BEV alone. The addition of BEV to radiation and TMZ in newly diagnosed GBM improved progression-free survival but did not improve overall survival. TMZ alone may be a reasonable approach in elderly GBM patients with poor performance status. Two Phase II trials with sunitinib and vatalanib showed a hint of activity in patients with recurrent or progressive meningiomas.

Journal Title: Expert review of anticancer therapy

PUBMED ID: 21339260

DOI: doi.org/10.1634/theoncologist.2010-0335

Titolo: Controversies in the adjuvant therapy of high-grade gliomas.

Autori: Holdhoff M., Grossman SA.

Data di Pubblicazione: 2011-2-23

Abstract: The 2-year survival rate of patients with glioblastoma accrued to research studies increased from 10% to nearly 40% from 2000 to 2010. These improvements began with the demonstration of a survival benefit when daily temozolomide was administered with 6 weeks of standard radiation and for 6 months thereafter. This treatment regimen is often associated with significant lymphopenia, thrombocytopenia, and progressive blood-brain barrier dysfunction that can result in clinical and radiologic deterioration without true tumor progression ("pseudoprogression"). With new evidence that combining this cytotoxic agent with radiation improves survival in this malignancy, many investigators have modified the regimen to further improve patient outcomes. These largely uncontrolled studies highlight controversies regarding the optimal therapy of this disease. This review focuses on the following selected controversies: (a) What is the appropriate temozolomide dose, schedule, and duration in the postradiation period? (b) How should other U.S. Food and Drug Administration-approved therapies (such as carmustine wafers and bevacizumab) be incorporated into this treatment regimen? (c) Should the results in glioblastoma be extrapolated to patients aged  $>70$  and to patients with lower grade gliomas? and (d) How should novel therapeutic approaches be added to rad

iation and temozolomide in clinical trials for patients with newly diagnosed glioblastoma?

Journal Title: The oncologist

PUBMED ID: 21319282

DOI: doi.org/10.1002/pbc.23006

Titolo: Impact of chemotherapy on disseminated low-grade glioma in children and adolescents: report from the HIT-LGG 1996 trial.

Autori: von Hornstein S., Kortmann RD., Pietsch T., Emser A., Warmuth-Metz M., Soerensen N., Straeter R., Graf N., Thieme B., Gnekow AK.

Data di Pubblicazione: 2011-2-15

Abstract: Complete MRI scan should be a standard diagnostic procedure in young children with hypothalamic-chiasmatic tumors especially if presenting with diencephalic syndrome. Dissemination in childhood LGG relates to impaired PFS. CT delays progression for responders. Multicenter studies have to evaluate the efficacy of extended treatment strategies in DLGG to improve outcome.

Journal Title: Pediatric blood & cancer

PUBMED ID: 21310734

DOI: doi.org/10.1093/neuonc/noq203

Titolo: Clinical trial end points for high-grade glioma: the evolving landscape.

Autori: Reardon DA., Galanis E., DeGroot JF., Cloughesy TF., Wefel JS., Lamborn KR., Lassman AB., Gilbert MR., Sampson JH., Wick W., Chamberlain MC., McDonald DR., Mehta MP., Vogelbaum MA., Chang SM., Van den Bent MJ., Wen PY.

Data di Pubblicazione: 2011-2-12

Abstract: To review the strengths and weaknesses of primary and auxiliary end points for clinical trials among patients with high-grade glioma (HGG). Recent advances in outcome for patients with newly diagnosed and recurrent HGG, coupled with the development of multiple promising therapeutics with myriad antitumor actions, have led to significant growth in the number of clinical trials for patients with HGG. Appropriate clinical trial design and the incorporation of optimal end points are imperative to efficiently and effectively evaluate such agents and continue to advance outcome. Growing recognition of limitations weakening the reliability of traditional clinical trial primary end points has generated increasing uncertainty of how best to evaluate promising therapeutics for patients with HGG. The phenomena of pseudoprogression and pseudoresponse have made imaging-based end points, including overall radiographic response and progression-free survival, problematic. Although overall survival is considered the "gold-standard" end point, recently identified active salvage therapies such as bevacizumab may diminish the association between presalvage therapy and overall survival. Finally, advances in imaging as well as the assessment of patient function and well being have strengthened interest in auxiliary end points assessing these aspects of patient care and outcome. Better appreciation of the strengths and limitations of primary end points will lead to more effective clinical trial strategies. Technical advances in imaging as well as improved survival for patients with HGG support the further development of auxiliary end points evaluating novel imaging approaches as well as measures of patient function and well being.

Journal Title: Neuro-oncology

PUBMED ID: 21297433

DOI: doi.org/10.1097/COC.0b013e318201a2b7

Titolo: Palliative reirradiation for progressive diffuse intrinsic pontine glioma.



Autori: Fontanilla HP., Pinnix CC., Ketonen LM., Woo SY., Vats TS., Rytting ME., Wolff JE., Mahajan A.

Data di Pubblicazione: 2011-2-8

Abstract: Reirradiation with chemotherapy may be feasible to improve symptoms and delay progression with minimal toxicity. Patients who are most likely to benefit may be those with prolonged response to initial therapy and a long interval since initial radiation.

Journal Title: American journal of clinical oncology

PUBMED ID: 21297126

DOI: doi.org/10.1093/neuonc/noq200

Titolo: MRI as a central component of clinical trials analysis in brainstem glioma: a report from the Pediatric Brain Tumor Consortium (PBTC).

Autori: Poussaint TY., Kocak M., Vajapeyam S., Packer RI., Robertson RL., Geyer R., Haas-Kogan D., Pollack IF., Vezina G., Zimmerman R., Cha S., Patay Z., Boyett JM., Kun LE.

Data di Pubblicazione: 2011-2-8

Abstract: We report MRI findings from 2 pediatric clinical trials of diffuse intrinsic brainstem glioma (BSG) incorporating concurrent radiation therapy (RT) with molecularly targeted agents (gefitinib and tipifarnib). We determined associations of MRI variables with progression-free survival and overall survival and investigated effects of treatment on these variables. MRI (including diffusion and perfusion) was done before treatment, every 8 weeks (first year), every 12 weeks (thereafter), and at the end of treatment or disease progression. Reduced tumor volume ( $P < .0001$ ) and tumor diffusion values ( $P < .0001$ ) were apparent on the first post-RT/drug studies. Decreases in tumor volume correlated with pre-RT volume ( $P < .0001$ ) and pre-RT diffusion values ( $P < .0001$ ); larger decreases were noted for tumors with higher volumes and diffusion values. Patients with larger pre-RT tumors had longer progression-free survival ( $P < .0001$ ). Patients with  $\geq 25\%$  decrease in tumor volume and diffusion values after RT had longer progression-free survival ( $P = .028$ ) and overall survival ( $P = .0009$ ). Enhancement at baseline and over time was significantly associated with shorter survival. Tumor diffusion values with baseline enhancement were significantly lower than those without ( $P = .0002$ ). RT of BSG is associated with decreased tumor volume and intralesional diffusion values; patients with  $\geq 25\%$  decrease in values post-RT had relatively longer survival intervals, apparently providing an early imaging-based surrogate for relative outcomes. Patients with larger tumors and greater decreases in tumor volume and diffusion values had longer survival intervals. Tumor enhancement was associated with shorter survival, lower tumor diffusion values (increased cellularity), and a smaller drop in diffusion values after RT ( $P = .006$ ). These associations justify continued investigation in other large clinical trials of brainstem glioma patients.

Journal Title: Neuro-oncology

PUBMED ID: 21292687

DOI: doi.org/10.1093/neuonc/noq199

Titolo: A phase II study of gefitinib and irradiation in children with newly diagnosed brainstem gliomas: a report from the Pediatric Brain Tumor Consortium.

Autori: Pollack IF., Stewart CF., Kocak M., Poussaint TY., Broniscer A., Banerjee A., Douglas JG., Kun LE., Boyett JM., Geyer JR.

Data di Pubblicazione: 2011-2-5

Abstract: This phase II study was designed to assess the safety and efficacy of gefitinib given with and following radiation therapy in children newly diagnosed with a poor prognosis brainstem glioma. Eligible patients were those with a previously untreated nondisseminated diffuse intrinsic brainstem glioma. Histological confirmation was not required, provided patients had a char

acteristic clinical history and MRI findings. Treatment consisted of gefitinib, administered orally, 250 mg/m<sup>2</sup>/day, during standard external beam radiotherapy, continuing for up to 13 monthly courses in the absence of disease progression or unacceptable toxicity. Toxicities, particularly intratumoral hemorrhage, were monitored. Pharmacokinetics and investigational imaging studies were performed in consenting patients. Forty-three eligible patients were included in the study. Therapy was well tolerated; only 4 patients were withdrawn from the study for dose-limiting toxicity after receiving therapy for 6, 9, 17, and 24 weeks. The 12- and 24-month progression-free survival rates were 20.9 ±5.6 % and 9.3 ±4%, respectively. Overall survival rates were 56.4 ±7.6% and 19.6 ±5.9%, respectively, which appear nominally superior to other contemporaneous Pediatric Brain Tumor Consortium trials. Three patients remain progression-free survivors with ≥36 months follow-up. The observation that a subset of children with this generally fatal tumor experienced long-term progression-free survival, coupled with recent observations regarding the molecular features of brainstem gliomas, raises the possibility that prospective molecular characterization may allow enrichment of treatment responders and improvement in outcome results in future studies of biologically targeted agents.

Journal Title: Neuro-oncology

PUBMED ID: 21282590

DOI: doi.org/10.1212/WNL.0b013e31820a0a8a

Titolo: Patterns of progression in patients with recurrent glioblastoma treated with bevacizumab.

Autori: Pope WB., Xia Q., Paton VE., Das A., Hambleton J., Kim HJ., Huo J., Brown MS., Goldin J., Cloughesy T.

Data di Pubblicazione: 2011-2-2

Abstract: Most patients treated with BEV or BEV+CPT-11 on BRAIN did not experience a change from baseline in radiographic characteristics of disease at the time of progression.

Journal Title: Neurology

PUBMED ID: 21241008

DOI: doi.org/10.1002/pbc.22967

Titolo: Visual outcome following chemotherapy for progressive optic pathway gliomas.

Autori: Shofty B., Ben-Sira L., Freedman S., Yalon M., Dvir R., Weintraub M., Toledano H., Constantini S., Kesler A.

Data di Pubblicazione: 2011-1-18

Abstract: The majority of our patients, who received chemotherapy for progressive OPG, experienced a decline in their visual function. New, more effective treatments are needed in order to preserve vision in this group.

Journal Title: Pediatric blood & cancer

PUBMED ID: 21240059

DOI: doi.org/10.1097/PAT.0b013e328340bb98

Titolo: The evolution of the histology in pleomorphic xanthoastrocytomas in children: a study of 15 cases.

Autori: Wu X., Bandopadhyay P., Ng J., Ashley D., Chow CW.

Data di Pubblicazione: 2011-1-18

Abstract: PXA should be considered in superficial cerebral tumours composed only of compact bundles of glial fibrillary acidic protein positive spindle cells with inconspicuous mitosis, even when the highly characteristic features of this tumour are not seen. The prominent variation in histology makes small biopsies difficult for diagnosis and assessing anaplasia. Patients with

non-anaplastic tumours can often be salvaged by more treatment for tumour progression.

Journal Title: Pathology

PUBMED ID: 21235315

DOI: doi.org/10.3171/2010.12.JNS10846

Titolo: Cortical ependymoma: an unusual epileptogenic lesion.

Autori: Van Gompel JJ., Koeller KK., Meyer FB., Marsh WR., Burger PC., Roncaroli F., Worrell GA., Giannini C.

Data di Pubblicazione: 2011-1-18

Abstract: Cortical ependymomas represent a rare type of ependymoma occurring superficially in the cortex. Morphologically, these tumors are protean, varying from classic to epithelioid, clear cell, and tanycytic. Some also exhibited features typical of AG. Most tumors were low grade and cured with resection. Anaplastic tumors occur and may recur locally despite provision of radiation therapy. Cortical ependymomas frequently, but not always, present with seizures, but despite their high association with epilepsy, none occurred in the temporal lobe in any of the authors' 9 patients. Overall, CEs appear to have a relatively favorable prognosis compared with other supratentorial ependymomas.

Journal Title: Journal of neurosurgery

PUBMED ID: 21233173

DOI: doi.org/10.2967/jnumed.110.081463

Titolo: Evaluation of 18F-FDG PET and MRI associations in pediatric diffuse intrinsic brain stem glioma: a report from the Pediatric Brain Tumor Consortium.

Autori: Zukotynski KA., Fahey FH., Kocak M., Alavi A., Wong TZ., Treves ST., Shulkin BL., Haas-Kogan DA., Geyer JR., Vajapeyam S., Boyett JM., Kun LE., Pousaint TY.

Data di Pubblicazione: 2011-1-15

Abstract: Children with BSG for which (18)F-FDG uptake involves at least half of the tumor appear to have poorer survival than children with uptake in less than 50% of the tumor. A larger independent study is needed to verify this hypothesis. Intense tracer uptake in the tumors, compared with gray matter, suggests decreased survival. Higher (18)F-FDG uptake within the tumor was associated with enhancement on MR images. Increased tumor cellularity as reflected by restricted MRI diffusion may be associated with increased (18)F-FDG uniformity throughout the tumor.

Journal Title: Journal of nuclear medicine : official publication, Society of Nuclear Medicine

PUBMED ID: 24213125

DOI: doi.org/10.3390/cancers3044061

Titolo: A Review of the Role of Re-Irradiation in Recurrent High-Grade Glioma (HGG).

Autori: Amichetti M., Amelio D.

Data di Pubblicazione: 2013-11-12

Abstract: Despite the use of more effective multimodal treatments in high-grade glioma (HGG), the outcome of patients affected by this disease is still dismal and recurrence is a very common event. Many therapeutic approaches, alone or combined (surgery, drugs, targeted agents, immunotherapy, radiotherapy, supportive therapy), are available in the clinical armamentarium so far. The attitude of physicians is increasingly interventionist, but recurrent HGG still remains a very difficult scenario to be treated. Radiotherapy with different re-irradiation techniques is increasingly proposed as a therapeutic option with interesting results, even though the resulting duration of response

nse is usually quite short. Most lesions re-recr locally, with inadequate identification and targeting of viable tumor being the most important cause of failure. Prognosis is affected by many patient-, tumor-, and treatment-associated prognostic factors. Radiotherapy is delivered with many advanced modalities: 3D-CRT, intensity-modulated radiation therapy, stereotactic fractionated radiotherapy, radiosurgery, and brachithrapy with or without chemotherapy administration. In order to evaluate the feasibility and efficacy of re-irradiation in this setting, we reviewed the PubMed and MEDLINE databases restricting the search to original reports published from January 1990 to June 2011. The search resulted in a total of 155 reports: 78 of them covering 2,688 patients treated with different irradiation modalities overall fulfilled the entry criteria. Radiation therapy demonstrated to be an acceptable option in recurrent HGG with good response rates and acceptable toxicity.

Journal Title: Cancers

PUBMED ID: 21187515

DOI: Mancante

Titolo: Bevacizumab and glioblastomas, a single-centre experience: how disease history and characteristics may affect clinical outcome.

Autori: Zustovich F., Lombardi G., Pastorelli D., Farina P., Furini L., Manara R., Dalla Palma M., Rotilio A., Nicoletto O., Zagonel V.

Data di Pubblicazione: 2010-12-29

Abstract: Although well-tolerated, the efficacy of bevacizumab was somewhat disappointing, possibly due to the high rate of secondary high-grade gliomas in the studied patient cohort and the late use of bevacizumab in the course of the disease.

Journal Title: Anticancer research

PUBMED ID: 21181283

DOI: doi.org/10.1007/s10354-010-0863-5

Titolo: [Drug therapy of patients with recurrent glioblastoma: is there any evidence?].

Autori: Pichler J., Marosi C.

Data di Pubblicazione: 2010-12-25

Abstract: Thorough consideration of the individual patient's characteristics to evaluate the best fitted treatment is warranted, preferentially in the context of an interdisciplinary tumour board.

Journal Title: Wiener medizinische Wochenschrift (1946)

PUBMED ID: 21177338

DOI: doi.org/10.1093/neuonc/noq177

Titolo: First-line temozolomide chemotherapy in progressive low-grade astrocytomas after radiotherapy: molecular characteristics in relation to response.

Autori: Taal W., Dubbink HJ., Zonnenberg CB., Zonnenberg BA., Postma TJ., Gijtenbeek JM., Boogerd W., Groenendijk FH., Kros JM., Kouwenhoven MC., van Marion R., van Heuvel I., van der Holt B., Bromberg JE., Sillevius Smitt PA., Dinjens WN., van den Bent MJ., van den Bent MJ.

Data di Pubblicazione: 2010-12-24

Abstract: Only a few studies examined the effect of temozolomide (TMZ) in recurrent low-grade astrocytoma (LGA) after surgery, none of which included a homogeneous and sufficiently sized group of patients with progression after radiotherapy (RT). We evaluated a cohort of 58 patients treated with TMZ for progression after RT of a previous LGA and investigated the relation between outcome and mutations in the IDH1, IDH2, and TP53 genes, O<sup>6</sup>-methylguanine-methyltransferase (MGMT) promoter methylation, trisomy of chromosome 7, and lo

ss of chromosomes 1p and 19q. All patients received first-line TMZ 200 mg/m<sup>2</sup>/day on days 1-5 every 4 weeks for a progressive LGA with a contrast-enhancing lesion on MRI after RT. Six months progression-free survival (PFS) was 67%, and the median overall survival was 14 months. An objective response was obtained in 54%. TP53 mutations and loss of chromosome 19q showed a borderline association with PFS, but none of the other molecular characteristics were correlated with the outcome to TMZ. Both a methylated MGMT promoter gene and IDH1 mutations were found in 86% of the tumor samples. A correlation was found between IDH1 mutations and MGMT promoter methylation (P < .001). Neither MGMT promoter methylation nor IDH1 mutations correlated with PFS, but the interval between the very first symptom of the LGA and the start of the TMZ was significantly longer in the patients with IDH1 mutations (P = .01) and a methylated MGMT promoter (P = .02). We conclude that MGMT promoter methylation and IDH1 mutations seem to predict survival from the time of diagnosis, but not PFS to TMZ.

Journal Title: Neuro-oncology

PUBMED ID: 21158519

DOI: doi.org/10.3109/02688697.2010.528473

Titolo: Case report: extracranial metastasis from gliosarcoma--the influence of immune system.

Autori: Rapp M., Felsberg J., Sorg RV., Gerharz CD., Sabel M.

Data di Pubblicazione: 2010-12-17

Abstract: Extracranial metastasis of malignant glioma is an extremely rare event. We report on a 67-year-old patient with a primary gliosarcoma that was treated by open resection. The concomitant radio-chemotherapy which followed induced an unusually severe and early leucocytopenia. Ten months after diagnosis, the patient presented with multiple metastases in the lung and the skeletal system. The clinical, radiological and neuropathological findings are described. In addition, we discuss the possible role of a compromised immune system in the development of extracranial glioma metastasis.

Journal Title: British journal of neurosurgery

PUBMED ID: 21148162

DOI: doi.org/10.1093/jjco/hyq224

Titolo: The correlation between promoter methylation status and the expression level of O6-methylguanine-DNA methyltransferase in recurrent glioma.

Autori: Suzuki T., Nakada M., Yoshida Y., Nambu E., Furuyama N., Kita D., Hayashi Y., Hayashi Y., Hamada J.

Data di Pubblicazione: 2010-12-15

Abstract: Our results give the evidence that the increase of O(6)-methylguanine-DNA methyltransferase mRNA expression caused by methylation changes in recurrence may be associated with chemoresistance in the recurrent glioma.

Journal Title: Japanese journal of clinical oncology

PUBMED ID: 21108437

DOI: doi.org/10.1002/pbc.22690

Titolo: A phase II study of metronomic oral topotecan for recurrent childhood brain tumors.

Autori: Minturn JE., Janss AJ., Fisher PG., Allen JC., Patti R., Phillips PC., Belasco JB.

Data di Pubblicazione: 2010-11-26

Abstract: Daily oral topotecan at a dose of 0.8 mg/m<sup>2</sup>/day can be safely administered to children with recurrent or refractory brain tumors. This regimen identified activity in recurrent PNET. The prolonged progression free survival (PFS) in two PNET patients justifies consideration of this regimen in more advanced clinical trials.

Journal Title: Pediatric blood & cancer

PUBMED ID: 21107549

DOI: doi.org/10.1007/s00234-010-0802-6

Titolo: MR perfusion and diffusion imaging in the follow-up of recurrent glioblastoma treated with dendritic cell immunotherapy: a pilot study.

Autori: Vrabec M., Van Cauter S., Himmelreich U., Van Gool SW., Sunaert S., De Vleeschouwer S., Suput D., Demaerel P.

Data di Pubblicazione: 2010-11-26

Abstract: The maximum lesional rCBV ratios and minimum ADC values in the contrast-enhancing area are potential radiological markers to differentiate between immune therapy-induced inflammatory response and recurrent glioblastoma tumour growth in glioblastoma patients treated with immune therapy.

Journal Title: Neuroradiology

PUBMED ID: 21072819

DOI: doi.org/10.1002/pbc.22868

Titolo: Bevacizumab and irinotecan in the treatment of children with recurrent/refractory medulloblastoma.

Autori: Aguilera DG., Goldman S., Fangusaro J.

Data di Pubblicazione: 2010-11-13

Abstract: Relapsed/refractory medulloblastoma (MB) has a poor outcome regardless of the treatment employed. Novel therapies are needed in an effort to improve survivals. We present two children with recurrent/refractory MB treated with bevacizumab and irinotecan both given every 2 weeks. One patient also received temozolamide. The first patient had stable disease and remains without progression after 30 months. The second patient had a near complete response that was sustained for 18 months. The regimen was well tolerated with minimal toxicity and provided prolonged progression-free survival in these two patients. Prospective clinical trials are needed to evaluate the effectiveness of this strategy.

Journal Title: Pediatric blood & cancer

PUBMED ID: 21069427

DOI: doi.org/10.1007/s11060-010-0452-x

Titolo: Recurrence in childhood medulloblastoma.

Autori: Warmuth-Metz M., Blashofer S., von Bueren AO., von Hoff K., Bison B., Pohl F., Kortmann RD., Pietsch T., Rutkowski S.

Data di Pubblicazione: 2010-11-12

Abstract: Thirty-eight consecutive children treated according to the HIT2000 and HIT91 studies for medulloblastoma who suffered 40 recurrence events were identified from a neuroradiological database. Relapse was associated with younger median age compared with all children treated on HIT2000. Eight patients relapsed with isolated local recurrence. There was no correlation with incomplete surgical removal or violation of the respective treatment protocol. Four patients were younger than 4 years at time of initial presentation and thus were not treated primarily with radiotherapy, suggesting that delayed radiotherapy might be a contributing factor. Meningeal dissemination was present in 32 events; 16 were located in the frontal region, 8 of which were isolated nodular frontal and frontobasal meningeal disease. Circumscribed meningeal recurrences were associated with better overall survival (OS) compared with diffuse, widespread recurrences. Isolated frontobasal meningeal relapses are a well-known phenomenon in medulloblastomas even years after treatment and have been correlated to an underdose of radiation in many literature reports. However, in our patients there was no correlation to possible treatment violations, indicating that inadequate radiation dose to the frontobasal region was unlikely to be a causative factor. Surgical technique varied due to

o the multicentric nature of our study, so position during surgery was not recognized as a predisposing factor for frontobasal recurrence.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 21038110

DOI: doi.org/10.1007/s11060-010-0444-x

Titolo: Treatment of children with recurrent high grade gliomas with a bevacizumab containing regimen.

Autori: Parekh C., Jubran R., Erdreich-Epstein A., Panigrahy A., Bluml S., Finlay J., Dhall G.

Data di Pubblicazione: 2010-11-2

Abstract: Children with recurrent high grade gliomas (HGG) have a dismal outcome with a median progression free survival (PFS) of 12 weeks. Adults with recurrent HGG treated with irinotecan and bevacizumab reportedly have a 63% response rate and a median PFS of 23 weeks. There is a paucity of corresponding published pediatric data. We retrospectively reviewed the records of patients less than 21 years of age with recurrent or progressive WHO grade 3-4 gliomas who were treated with bevacizumab containing regimens at our institution between January 2006 and September 2008. We identified eight patients. Six out of eight patients received irinotecan, temozolomide and bevacizumab, one patient received irinotecan and bevacizumab, and one patient received CCNU and bevacizumab. Three patients had stable disease for 30-93 weeks. The remaining five patients developed progressive disease within 17 weeks. The median PFS was 15 weeks and the 6-month PFS was 38%. Contrast enhancing disease responded or remained stable in five out of seven patients whereas non-enhancing disease progressed in three out of four patients. New distant non-enhancing lesions developed in three patients. The most common side effects included diarrhea, vomiting, thrombocytopenia and neutropenia. Bevacizumab was well tolerated when used in combination with conventional chemotherapy (irinotecan in most cases). PFS in our cohort was much shorter and the response rate was inferior in this small cohort of patients when compared with published adult data. However, bevacizumab containing regimens might be effective in a subset of pediatric patients, especially those with predominantly contrast-enhancing disease.

Journal Title: Journal of neuro-oncology

PUBMED ID: 20952169

DOI: doi.org/10.1016/j.clon.2010.09.007

Titolo: Carboplatin chemotherapy in patients with recurrent high-grade glioma.

Autori: Murray LJ., Bridgewater CH., Levy D.

Data di Pubblicazione: 2010-10-19

Abstract: Single-agent carboplatin has modest activity in patients with recurrent HGG who have received at least two lines of chemotherapy. The overall time to progression is short and over two-thirds of patients had to discontinue treatment due to progressive disease. Among the small proportion of patients achieving stable disease or a partial response to treatment, the median survival is improved. More effective but well tolerated regimens are required for this patient population.

Journal Title: Clinical oncology (Royal College of Radiologists (Great Britain))

PUBMED ID: 20925951

DOI: doi.org/10.1186/1471-2407-10-533

Titolo: Randomised phase I/II study to evaluate carbon ion radiotherapy versus fractionated stereotactic radiotherapy in patients with recurrent or progressive gliomas: the CINDERELLA trial.

Autori: Combs SE., Burkholder I., Edler L., Rieken S., Habermehl D., Jäkel O., Haberer T., Haselmann R., Unterberg A., Wick W., Debus J.  
Data di Pubblicazione: 2010-10-8  
Abstract: NCT01166308.  
Journal Title: BMC cancer

PUBMED ID: 20921456  
DOI: doi.org/10.1200/JCO.2010.30.3545  
Titolo: Phase I study of vandetanib during and after radiotherapy in children with diffuse intrinsic pontine glioma.  
Autori: Broniscer A., Baker JN., Tagen M., Onar-Thomas A., Gilbertson RJ., D avidoff AM., Pai Panandiker AS., Panandiker AP., Leung W., Chin TK., Stewart CF., Kocak M., Rowland C., Merchant TE., Kaste SC., Gajjar A.  
Data di Pubblicazione: 2010-10-6  
Abstract: The recommended phase II dose of vandetanib in children is 145 mg/m<sup>2</sup> per day. Close monitoring and management of hypertension is required, particularly for patients receiving corticosteroids.  
Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 20811928  
DOI: doi.org/10.1007/s11060-010-0371-x  
Titolo: Feasibility study of 21-day-on/7-day-off temozolomide in children with brain tumors.  
Autori: Ridola V., Barone G., Lazzareschi I., Ruggiero A., Rizzo D., Riccardi R.  
Data di Pubblicazione: 2010-9-3  
Abstract: Temozolomide (TMZ) is an oral alkylating agent with proven antitumor activity in preclinical and clinical studies in adults with high-grade glioma (HGG). However, only limited efficacy has been reported in children with HGG using the 5-day schedule. This study investigated the safety of administering TMZ to children and adolescents with brain tumors over an extended period. Extended schedules have been proven to overcome chemoresistance without any major toxicity. The toxicity of TMZ, administered at 70 mg/m<sup>2</sup>/day orally for 21 consecutive days every 28 days, was assessed in children with brain tumors. A total of 156 courses of TMZ were given to 17 patients (median age 12.5 years, range 1-17 years), who were recruited into the study. Eleven patients had progressive or relapsing disease, and six patients were newly diagnosed. In this cohort no cases of toxic death or nonhematological toxicity were reported. In comparison with the 5-day schedule, thrombocytopenia and neutropenia were noted to be less frequent. Grades 3 and 4 lymphopenia occurred in 10.8 and 22.4% of courses, respectively; among the lymphopenic patients there was one case of disseminated zoster (meningoencephalitis and cutaneous involvement), one case of rotavirus gastroenteritis, and two cases of herpetic stomatitis reported. The objective response rate was 11.8%. Overall, 82.3% of patients showed stable disease. The prolonged TMZ schedule appeared to be well tolerated, with few cases of neutropenia or thrombocytopenia recorded. Nevertheless, prolonged exposure to TMZ was associated with lymphopenia and may lead to a higher rate of viral infections.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 20809868  
DOI: doi.org/10.1517/14728222.2010.515980  
Titolo: Taking aim at Mer and Axl receptor tyrosine kinases as novel therapeutic targets in solid tumors.  
Autori: Linger RM., Keating AK., Earp HS., Graham DK.  
Data di Pubblicazione: 2010-9-3



Abstract: Axl and Mer mediate multiple oncogenic phenotypes and activation of these RTKs constitutes a mechanism of chemoresistance in a variety of solid tumors. Targeted inhibition of these RTKs may be effective as anti-tumor and/or anti-metastatic therapy, particularly if combined with standard cytotoxic therapies.

Journal Title: Expert opinion on therapeutic targets

PUBMED ID: 20736948

DOI: doi.org/10.1038/sj.bjc.6605796

Titolo: MGMT gene promoter methylation correlates with tolerance of temozolomide treatment in melanoma but not with clinical outcome.

Autori: Hassel JC., Sucker A., Edler L., Kurzen H., Moll I., Stresemann C., Spieth K., Mauch C., Rass K., Dummer R., Schadendorf D.

Data di Pubblicazione: 2010-8-26

Abstract: In advanced melanoma MGMT promoter, methylation correlates with tolerance of therapy, but not with clinical outcome.

Journal Title: British journal of cancer

PUBMED ID: 20730617

DOI: doi.org/10.1007/s11060-010-0354-y

Titolo: Hepatic encephalopathy after treatment with temozolomide.

Autori: Goldbecker A., Tryc AB., Raab P., Worthmann H., Herrmann J., Weissenborn K.

Data di Pubblicazione: 2010-8-24

Abstract: Temozolomide in combination with radiation has been in use for more than 5 years for the therapy of glioblastoma. Known adverse effects concerning the gastrointestinal system are elevation of liver enzymes. We present the case of a patient treated with temozolomide who developed severe cholestatic liver damage and consecutive hepatic encephalopathy. Neurological symptoms were mistaken as being caused by focal brain damage for more than 9 months. After the correct diagnosis had been made and the treatment had been started, the patient's condition ameliorated. In conclusion, neurological deficits in patients with known brain lesion should not be attributed automatically to the pre-existing damage even if it is progressive but should be examined carefully, also including toxic and metabolic encephalopathies into the differential diagnosis. Furthermore, new side effects of drugs have to be considered. At least this case might lead to a closer monitoring of liver enzymes during temozolomide therapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 20724193

DOI: doi.org/10.1016/j.canrad.2010.03.021

Titolo: [Systematic review of stereotactic radiotherapy for high-grade gliomas].

Autori: Clavier JB., Voirin J., Kehrli P., Noël G.

Data di Pubblicazione: 2010-8-21

Abstract: The purpose of this literature systematic review was the use of stereotactic radiotherapy in glioma. Research was performed in Medline/PubMed and associated references found in published articles without publication date limit. The quality of series is variable and many biases can be evidenced. Only two randomized trials have been published using stereotactic radiotherapy for up-front treatment. There is a lack of evidence of survival advantages to use this treatment at the time of diagnosis or relapse. There is also insufficient evidence regarding the benefice/harms in the use of stereotactic fractionated radiation therapy for patients with glioma. No recommendations can be enounced. Stereotactic irradiation as boost in primary diagnosed glioma or relapsed tumour is not associated with survival improvement. For rel

apsed patients, treatment needs to be discussed according to the other treatment options.

Journal Title: Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique

PUBMED ID: 20694800

DOI: doi.org/10.1007/s11060-010-0334-2

Titolo: High dose methotrexate for pediatric high grade glioma: results of the HIT-GBM-D pilot study.

Autori: Wolff JE., Kortmann RD., Wolff B., Pietsch T., Peters O., Schmid HJ., Rutkowski S., Warmuth-Metz M., Kramm C.

Data di Pubblicazione: 2010-8-10

Abstract: We conducted a phase II study to test methotrexate (5 g/m<sup>2</sup>), as a single agent prior to radiochemotherapy for pediatric high-grade glioma and diffuse intrinsic pontine glioma. Thirty patients (19 male, median age 10.8) were enrolled. Tumors were located as follows: cortex 10, pons 7, other 13. Tumor resection was classified as gross total in 6, subtotal in 6, partial in 4, biopsy in 11 and not performed in 3. WHO grading of the histology was: IV: 11, III: 12 and II: 3. Patients received methotrexate 5 g/m<sup>2</sup> in 24-hour infusions on days 1 and 15. Subsequently 54 Gy radiation was administered with simultaneous chemotherapy including cisplatin, etoposide, vincristine and ifosfamide as previously described. Eight 6-weeks cycles of maintenance chemotherapy consisted of vincristine 1.5 mg/m<sup>2</sup> on days 1, 8 and 15; lomustine 100 mg/m<sup>2</sup> on day 2 and prednisone 40 mg/kg on days 1-17. Event-free survival rates in the whole group of 30 patients were: 43, 20, and 13% after 1, 2 and 5 years, respectively. The response evaluation after methotrexate was available in 19 of the 24 patients who started treatment with measurable disease: CR: 0, PR: 1, SD 18, PD: 0. After radiochemotherapy the response of 24 patients with measurable disease was CR: 1, PR 10, SD 12, PD 1. Both response and event-free survival were superior to the control group of 330 patients treated in various protocols of the same cooperative group. In subgroup analyses the use of dexamethasone during early treatment was linked to poor event free survival. Giving two cycles of high-dose methotrexate prior to radiochemotherapy was feasible, and the approach was taken forward to a randomized phase III trial.

Journal Title: Journal of neuro-oncology

PUBMED ID: 20683757

DOI: doi.org/10.1007/s11060-010-0325-3

Titolo: Phase II trial of ritonavir/lopinavir in patients with progressive or recurrent high-grade gliomas.

Autori: Ahluwalia MS., Patton C., Stevens G., Tekautz T., Angelov L., Vogelbaum MA., Weil RJ., Chao S., Elson P., Suh JH., Barnett GH., Peereboom DM.

Data di Pubblicazione: 2010-8-5

Abstract: Current therapies for recurrent or progressive high-grade gliomas (HGG, WHO grade 3-4) produce a 6-month progression-free survival of only 10-25%. Migration and invasion by HGG is mediated in part by matrix metalloproteinases (MMPs) which promote remodeling of the extracellular matrix. Several HIV protease inhibitors (HIVPI) decrease the expression of MMPs in astrocytes and microglia. Given these mechanisms of antitumor activity of HIVPI, we evaluated the efficacy of ritonavir/lopinavir, a combination HIVPI, in patients with progressive or recurrent HGG in an open label phase II trial. Nineteen patients were treated in this study. Patients received ritonavir/lopinavir (400 mg/100 mg) orally twice daily. All patients were treated until progression of disease or unacceptable toxicity. A complete response was seen in one patient (5%). Three patients (16%) had stable disease as the best response. Fifteen patients (79%) had progressive disease. The 6-month progression free survival (PFS(6)) was 11% (2 of 19 patients). Ritonavir/lopinavir was well tolerated.

olerated in patients with heavily pretreated refractory HGG, and no grade 3 or 4 toxicity was seen. The activity at the dose and schedule used in this study, however, was modest and the study did not meet its efficacy endpoint.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 20672934

DOI: doi.org/10.3171/2010.5.PEDS09553

Titolo: Ependymoma of the spinal cord in children and adolescents: a retrospective series from the HIT database.

Autori: Benesch M., Weber-Mzell D., Gerber NU., von Hoff K., Deinlein F., Krauss J., Warmuth-Metz M., Kortmann RD., Pietsch T., Driever PH., Quehenberger F., Urban C., Rutkowski S.

Data di Pubblicazione: 2010-8-3

Abstract: Gross-total resection is the mainstay of treatment for patients with primary spinal cord ependymoma and may be achieved in about 50% of the patients using modern surgical techniques. Primary adjuvant treatment was commonly used in children with spinal cord ependymoma irrespective of the extent of resection or tumor grade. The impact of adjuvant treatment on progression-free and overall survival has to be investigated in a prospective trial.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 20656474

DOI: doi.org/10.1016/j.ejca.2010.06.115

Titolo: A multi-centre Canadian pilot study of metronomic temozolomide combined with radiotherapy for newly diagnosed paediatric brainstem glioma.

Autori: Sharp JR., Bouffet E., Stempak D., Gammon J., Stephens D., Johnston DL., Eisenstat D., Hukin J., Samson Y., Bartels U., Tabori U., Huang A., Baruchel S.

Data di Pubblicazione: 2010-7-27

Abstract: Chemoradiotherapy with metronomic dosing of TMZ showed similar toxicity to previous TMZ regimens, and does not appear to improve survival in paediatric DIBSG.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 20632556

DOI: doi.org/10.1118/1.3425792

Titolo: Significant dose can be lost by extended delivery times in IMRT with x rays but not high-LET radiations.

Autori: Joiner MC., Mogili N., Marples B., Burmeister J.

Data di Pubblicazione: 2010-7-17

Abstract: Prolonged delivery times of photon fractions could have a significant impact on treatment outcome especially for tumors with a low alpha/beta ratio and short repair halftime. These effects are significant at delivery times commonly associated with IMRT and are variable with cell type. X-ray IMRT should therefore always be planned to minimize dose-fraction delivery time. However, if IMRT treatments are delivered with high-LET radiation, this considerably reduces the dependence of the biological effect on fraction delivery time even out to 2 h.

Journal Title: Medical physics

PUBMED ID: 20586629

DOI: doi.org/10.1043/2009-0015-OA.1

Titolo: Myelodysplastic syndromes arising in patients with germline TP53 mutation and Li-Fraumeni syndrome.

Autori: Talwalkar SS., Yin CC., Naeem RC., Hicks MJ., Strong LC., Abruzzo LV

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Data di Pubblicazione: 2010-7-1

Abstract: Patients with LFS may develop MDS, which is most likely therapy-related and is associated with cytogenetic markers of poor prognosis.

Journal Title: Archives of pathology & laboratory medicine

PUBMED ID: 20564393

DOI: doi.org/10.1002/cncr.25035

Titolo: Dose-dense temozolomide regimens: antitumor activity, toxicity, and immunomodulatory effects.

Autori: Neyns B., Tosoni A., Hwu WJ., Reardon DA.

Data di Pubblicazione: 2010-6-22

Abstract: Temozolomide is an oral alkylating agent with established antitumor activity in patients with primary brain tumors and melanoma. The originally approved temozolomide dosing regimen is 150 to 200 mg/m<sup>2</sup> per day (Days 1 to 5 every 28-day cycle [5 of 28 days]). However, extended dosing regimens (eg, 7 of 14 days, 21 of 28 days, 6 of 8 weeks, or continuously daily) allow for administration of a higher cumulative dose per cycle and have been shown to deplete O(6)-methylguanine-DNA methyltransferase, which may enhance cytotoxic activity. This article reviews efficacy and safety data from studies that investigated dose-dense temozolomide regimens in patients with recurrent glioma and advanced metastatic melanoma. The clinical benefits of these dose-dense regimens compared with the standard 5 of 28-day regimen have yet to be established. Although the toxicity profile of dose-dense temozolomide is generally similar to that of the standard 5 of 28-day regimen, it is associated with an increased incidence and severity of lymphocytopenia. The clinical management of temozolomide-associated lymphodepletion and the potential risks and benefits of extended dosing with temozolomide are discussed. Preclinical and clinical evidence suggests that temozolomide-associated lymphodepletion may enhance the host immune response to tumor-associated antigens and/or immunotherapy and may overcome tumor-mediated immunosuppression. Further studies exploring the clinical implications of lymphodepletion are warranted.

Journal Title: Cancer

PUBMED ID: 20558056

DOI: doi.org/10.1016/j.ejca.2010.05.004

Titolo: Phase I study of topotecan in combination with temozolomide (TOTEM) in relapsed or refractory paediatric solid tumours.

Autori: Rubie H., Geoerger B., Frappaz D., Schmitt A., Leblond P., Ndiaye A., Aerts I., Le Deley MC., Gentet JC., Paci A., Chastagner P., Dias N., Djafari L., Pasquet M., Chatelut E., Landman-Parker J., Corradini N., Vassal G.

Data di Pubblicazione: 2010-6-19

Abstract: The RD for the combination is TMZ 150 mg/m<sup>2</sup>/d and TPT 0.75 mg/m<sup>2</sup>/d with dose-limiting haematological toxicity. The observed activity deserves further evaluation in paediatric malignancies.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 20541421

DOI: doi.org/10.1016/j.jocn.2009.12.009

Titolo: Carboplatin and etoposide combined with bevacizumab for the treatment of recurrent glioblastoma multiforme.

Autori: Francesconi AB., Dupre S., Matos M., Martin D., Hughes BG., Wyld DK., Lickliter JD.

Data di Pubblicazione: 2010-6-15

Abstract: Relapsed glioblastoma multiforme (GBM) responds poorly to standard therapies. Vascular endothelial growth factor (VEGF) is implicated in the development of GBM and the anti-VEGF monoclonal antibody bevacizumab has shown early clinical promise against malignant glioma. We treated six patients with

h recurrent GBM using bevacizumab combined with carboplatin and etoposide chemotherapy (ACE regimen). Toxicity was that expected for carboplatin and etoposide alone, except for an ischemic stroke in one patient. We observed partial responses in five patients and one responding patient developed extensive tumour necrosis after 2 cycles of treatment. Median progression-free and overall survival was 19 and 29.9 weeks, respectively. Four responding patients developed recurrence, which was characterized by markedly less peri-tumoral edema, mass effect and necrosis compared with tumours at baseline. Two patients developed local extracranial extension. In conclusion, ACE was active in recurrent GBM and was mostly well tolerated.

Journal Title: Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia

PUBMED ID: 20539238

DOI: doi.org/10.1097/MPH.0b013e3181e34138

Titolo: Intraventricular glioblastoma multiforme: a pediatric case report.

Autori: Sarsilmaz A., Gelal F., Apaydin M., Varer M., Bezircioglu H., Rezanko T.

Data di Pubblicazione: 2010-6-12

Abstract: Glioblastoma multiforme (GBM) is the most common lethal primary central nervous system tumor in adults. GBM is rarely seen in childhood and adolescence as primary intraventricular tumors. Few cases of solitary intraventricular GBM in adolescence have been reported to date. We report a 16-year-old boy with progressive disorientation, diffuse headache, vomiting, and increased intracranial pressure. Computed tomography and magnetic resonance imaging confirmed that the tumor filled posterior body and occipital horn of the left lateral ventricle and also invaded the surrounding parenchyma. Incomplete removal of the lesion was achieved and a pathologic diagnosis of GBM was carried out. We present a case with an uncommon subtype of glial tumor (GBM) in childhood located in a very rare site. The clinical course, radiologic findings, and possible treatment regimens are reviewed.

Journal Title: Journal of pediatric hematology/oncology

PUBMED ID: 20538454

DOI: doi.org/10.1016/j.ejca.2010.05.016

Titolo: Phase I study of temozolomide combined with oral etoposide in children with recurrent or progressive medulloblastoma.

Autori: Ruggiero A., Rizzo D., Attinà G., Lazzareschi I., Mastrangelo S., Maurizi P., Migliorati R., Bertolini P., Pastore M., Colosimo C., Riccardi R.

Data di Pubblicazione: 2010-6-12

Abstract: The recommended phase II dose in children is TMZ 150 mg/m<sup>2</sup> on days 1-5 and VP-16 50 mg/m<sup>2</sup> on days 1-10 every 28 d. The combination was well tolerated and demonstrated antitumour activity.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 20511183

DOI: doi.org/10.1093/neuonc/noq008

Titolo: Prolonged survival for patients with newly diagnosed, inoperable glioblastoma with 3-times daily ultrafractionated radiation therapy.

Autori: Beauchesne P., Bernier V., Carnin C., Taillandier L., Djabri M., Martin L., Michel X., Maire JP., Khalil T., Kerr C., Gorlia T., Stupp R., Pedoux R.

Data di Pubblicazione: 2010-6-1

Abstract: Ultrafractionation of radiation therapy is a novel regimen consisting of irradiating tumors several times daily, delivering low doses (<0.75 Gy) at which hyperradiosensitivity occurs. We recently demonstrated the high efficiency of ultrafractionated radiotherapy (RT) on glioma xenografts and r

report here on a phase II clinical trial to determine the safety, tolerability, and efficacy of an ultrafractionation regimen in patients with newly and inoperable glioblastoma (GBM). Thirty-one patients with histologically proven, newly diagnosed, and unresectable supratentorial GBM (WHO grade IV) were enrolled. Three daily doses of 0.75 Gy were delivered at least 4 hours apart, 5 days per week over 6-7 consecutive weeks (90 fractions for a total of 67.5 Gy). Conformal irradiation included the tumor bulk with a margin of 2.5 cm. The primary end points were safety, toxicity, and tolerability, and the secondary end points were overall survival (OS) and progression-free survival (PFS). Multivariate analysis was used to compare the OS and PFS with the EORTC-NCIC trial 26981-22981/CE.3 of RT alone vs radiation therapy and temozolomide (TMZ). The ultrafractionation radiation regimen was safe and well tolerated. No acute Grade III and/or IV CNS toxicity was observed. Median PFS and OS from initial diagnosis were 5.1 and 9.5 months, respectively. When comparing with the EORTC/NCIC trial, in both PFS and OS multivariate analysis, ultrafractionation showed superiority over RT alone, but not over RT and TMZ. The ultrafractionation regimen is safe and may prolong the survival of patients with GBM. Further investigation is warranted and a trial associating ultrafractionation and TMZ is ongoing.

Journal Title: Neuro-oncology

PUBMED ID: 20479404

DOI: doi.org/10.1200/JCO.2009.26.8789

Titolo: Lack of efficacy of bevacizumab plus irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a Pediatric Brain Tumor Consortium study.

Autori: Gururangan S., Chi SN., Young Poussaint T., Onar-Thomas A., Gilbertson RJ., Vajapeyam S., Friedman HS., Packer RJ., Rood BN., Boyett JM., Kun LE.

Data di Pubblicazione: 2010-5-19

Abstract: BVZ plus CPT-11 was well-tolerated but had minimal efficacy in children with recurrent malignant glioma and brainstem glioma.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 20464625

DOI: doi.org/10.1007/s11060-010-0197-6

Titolo: Nitrosourea-based chemotherapy for low grade gliomas failing initial treatment with temozolomide.

Autori: Kaloshi G., Sierra del Rio M., Ducray F., Psimaras D., Idbaih A., Liguire-Donadey F., Taillibert S., Houillier C., Dehais C., Omuro A., Sanson M., Delattre JY., Hoang-Xuan K.

Data di Pubblicazione: 2010-5-14

Abstract: There is a growing evidence of using Temozolomide as upfront therapy for progressive low grade gliomas. No data exist on the efficacy of nitrosoureas as an alternative to radiotherapy in those patients who progress after Temozolomide. We retrospectively reviewed 30 patients with median age of 46 years. Twenty-one patients had pure oligodendrogliomas. Thirteen patients had a non-enhancing tumor at progression after Temozolomide. The chromosomes 1p/19q were co-deleted in 5 cases and retained in 10 cases. Response rate was 10% (3 minor responses achieved in non-enhancing tumors). Tolerance was acceptable (17% grade III and IV myelosuppression). Median PFS was 6.5 months. Median OS from start of salvage treatment was 23.4 months. Tumors without contrast enhancement demonstrated a better prognosis than those with contrast enhancement both in term of PFS ( $P = 0.0003$ ) and OS ( $P = 0.0006$ ). Chromosome 1p/19q codeletion was not predictive for objective response to salvage treatment but correlated with a better PFS ( $P = 0.02$ ). In conclusion, salvage NU chemotherapy provide disappointing results in TMZ-pretreated low grade gli

omas (LGG), which should be treated in priority by conventional radiotherapy especially in LGG that display contrast enhancement at progression.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 20458050

DOI: doi.org/10.1200/JCO.2009.26.3988

Titolo: Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma.

Autori: Batchelor TT., Duda DG., di Tomaso E., Ancukiewicz M., Plotkin SR., Gerstner E., Eichler AF., Drappatz J., Hochberg FH., Benner T., Louis DN., Cohen KS., Chea H., Exarhopoulos A., Loeffler JS., Moses MA., Ivy P., Sorensen AG., Wen PY., Jain RK.

Data di Pubblicazione: 2010-5-12

Abstract: Cediranib monotherapy for recurrent glioblastoma is associated with encouraging proportions of radiographic response, 6-month progression-free survival, and a steroid-sparing effect with manageable toxicity. We identified early changes in circulating molecules as potential biomarkers of response to cediranib. The efficacy of cediranib and the predictive value of these candidate biomarkers will be explored in prospective trials.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 20446099

DOI: doi.org/10.1007/s00701-010-0674-x

Titolo: Leptomeningeal dissemination of a pediatric neoplasm with 1p19q deletion showing mixed immunohistochemical features of an oligodendroglioma and neurocytoma.

Autori: Rhiew RB., Manjila S., Lozen A., Guthikonda M., Sood S., Kupsky WJ.

Data di Pubblicazione: 2010-5-7

Abstract: Leptomeningeal dissemination of an oligodendroglioma is rarely reported in the neurosurgical literature, especially in cases with a classical 1p19q deletion. The authors describe a case wherein a 1p19q deletion in a disseminated tumor with mixed immunohistochemical features of oligodendroglioma and neurocytoma was encountered and treated. Stereotactic right frontal craniotomy was undertaken for obtaining definitive histological diagnosis. The results revealed a neuroectodermal neoplasm with histologic and immunohistochemical features of oligodendroglioma and neurocytoma. FISH analysis confirmed classical 1p19q deletion. The patient was treated postoperatively with chemotherapy and radiation therapy. He showed good clinical response and remains alive 16 months after diagnosis.

Journal Title: Acta neurochirurgica

PUBMED ID: 20440540

DOI: doi.org/10.1007/s11060-010-0200-2

Titolo: Efficacy and safety of bevacizumab in active brain metastases from non-small cell lung cancer.

Autori: De Braganca KC., Janjigian YY., Azzoli CG., Kris MG., Pietanza MC., Nolan CP., Omuro AM., Holodny AI., Lassman AB.

Data di Pubblicazione: 2010-5-5

Abstract: Bevacizumab is effective for the treatment of non-small cell lung cancer (NSCLC). Ongoing trials are exploring the safety of bevacizumab in patients with inactive, previously treated brain metastases. However, bevacizumab safety and efficacy in the treatment of active brain metastases is unknown. Bevacizumab received accelerated FDA approval for progressive glioblastoma, a primary brain tumor, because of high response rates and low incidence of intracranial hemorrhage. We retrospectively identified patients treated with

ith bevacizumab for active (treatment naïve or progressive) central nervous system (CNS) metastases from NSCLC. MRI scans performed at least 6 weeks after initiating bevacizumab were assessed for response. There were six patients, four women and two men with a median age of 60 years (range 59-77) at initiation of bevacizumab. Five patients had progressive CNS metastases despite prior treatment including surgery, radiotherapy, and/or chemotherapy; one patient had treatment-naïve brain metastases. Two patients had leptomeningeal metastases, isolated or coexistent with parenchymal brain metastases in one patient each. Bevacizumab was administered alone to one patient and in combination with various cytotoxic chemotherapies in the others. Toxicity included an asymptomatic (Grade 1) intra-tumoral hemorrhage which occurred in one of three patients receiving concurrent anticoagulation with bevacizumab. There was no recurrent CNS bleeding in two patients with a prior history of such hemorrhage. Best CNS response (RECIST) was partial in two, stable disease in three, and progression in one. Median progression-free survival (PFS) was 7.8 months and median overall survival (OS) was 14.1 months following initiation of bevacizumab. Clinical benefit was also observed in the form of improved symptoms and reduced corticosteroid requirements. Bevacizumab should be used with caution in patients with active CNS metastases pending additional safety data. This series suggests bevacizumab may be safe and effective for progressive brain metastases from NSCLC and deserves further study.

Journal Title: Journal of neuro-oncology

PUBMED ID: 20425045

DOI: doi.org/10.1007/s10014-010-0265-9

Titolo: Prognostic value of WT1 protein expression level and MIB-1 staining index as predictor of response to WT1 immunotherapy in glioblastoma patients .

Autori: Chiba Y., Hashimoto N., Tsuboi A., Rabo C., Oka Y., Kinoshita M., Kagawa N., Oji Y., Sugiyama H., Yoshimine T.

Data di Pubblicazione: 2010-4-29

Abstract: The use of Wilms' tumor 1 (WT1) immunotherapy is considered to be an innovative approach for the treatment of malignant gliomas. Because of its novelty, tools that can accurately predict response to this therapy are still lacking. In this article, we investigated the role of WT1 protein expression level (score 1-4) and MIB-1 staining index in predicting survival outcome after therapy in patients with recurrent or progressive glioblastoma multiforme. Tumor samples from 37 patients enrolled in a phase II clinical trial on WT1 immunotherapy were immunohistochemically analyzed for WT1 levels and MIB-1 index. Results showed that median progression-free survival (PFS) was longer in the WT1 high expression group (score 3 and 4) compared with that of the low expression group (score 1 and 2) (20.0 weeks vs. 8.0 weeks;  $P = 0.022$ ), and that the median overall survival (OS) was likewise longer in the former compared to the latter group (54.4 weeks vs. 28.4 weeks;  $P = 0.035$ ). Furthermore, within the WT1 high expression group, tumors with intermediate staining intensity (WT1 score 3) have both the longest median PFS and OS, 24.4 weeks and 69.4 weeks, respectively. On the other hand, no significant correlation was noted between MIB-1 staining index and survival. In conclusion, our study has shown that WT1 protein expression level, not MIB-1 staining index, can be used as a prognostic marker to foretell outcome after immunotherapy, and that patients whose tumors have intermediate WT1 expression have the best survival outcome.

Journal Title: Brain tumor pathology

PUBMED ID: 20368564

DOI: doi.org/10.1200/JCO.2009.25.3971

Titolo: Parametric response map as an imaging biomarker to distinguish progression from pseudoprogression in high-grade glioma.



Autori: Tsien C., Galbán CJ., Chenevert TL., Johnson TD., Hamstra DA., Sundgren PC., Junck L., Meyer CR., Rehemtulla A., Lawrence T., Ross BD.

Data di Pubblicazione: 2010-4-7

Abstract: PRM(rCBV) at week 3 during chemoradiotherapy is a potential early imaging biomarker of response that may be helpful in distinguishing pseudoprogression from true progression in patients with high-grade glioma.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 20363768

DOI: doi.org/10.1093/neuonc/noq033

Titolo: Bevacizumab in recurrent high-grade pediatric gliomas.

Autori: Narayana A., Kunnakkat S., Chacko-Mathew J., Gardner S., Karajannis M., Raza S., Wisoff J., Weiner H., Harter D., Allen J.

Data di Pubblicazione: 2010-4-6

Abstract: Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has shown promise in treating recurrent adult high-grade glioma (HGG). However, there is very little data on recurrent or progressive pediatric HGG treated with bevacizumab. We report the results of a single institution experience using bevacizumab and irinotecan in children who relapsed or progressed following standard therapy. Twelve pediatric patients with recurrent or progressive HGG received bevacizumab at 10 mg/kg every 2 weeks with irinotecan at 125 mg/m<sup>2</sup>. Magnetic resonance imaging (MRI) was performed prior to therapy and every 8 weeks subsequently. Ten patients had supratentorial HGG; 2 had DIPG. Radiological responses were defined according to MacDonald's criteria. Progression-free survival (PFS), overall survival (OS), and toxicities were analyzed. Ten (83.3%) patients tolerated bevacizumab without serious toxicity. Therapy was discontinued in 1 patient because of anaphylaxis. Another patient developed grade III delayed wound healing and deep vein thrombosis. Two patients (16.7%) experienced a partial response after the first MRI. No complete radiographic responses were seen. Stable disease was noted in 4 (33.3%) patients. The median PFS and OS were 2.25 and 6.25 months, respectively. A diffuse invasive recurrence pattern was noted in 5 (45.5%) patients. Treatment tolerance, toxicity, and recurrence profiles were comparable to adult HGG patients treated with bevacizumab. However, the radiological response rate, response duration, and survival appeared inferior in pediatric patients. Genetic differences in pediatric gliomas might account for this difference.

Journal Title: Neuro-oncology

PUBMED ID: 20352473

DOI: doi.org/10.1007/s11060-010-0159-z

Titolo: Natural history and management of low-grade glioma in NF-1 children.

Autori: Hernáiz Driever P., von Hornstein S., Pietsch T., Kortmann R., Warmuth-Metz M., Emser A., Gnekow AK.

Data di Pubblicazione: 2010-3-31

Abstract: Pediatric neurofibromatosis type 1 (NF-1) patients are prone to developing low-grade glioma (LGG). The HIT-LGG study 1996 aimed to observe the natural history of pediatric LGG and to postpone irradiation in younger children by using carboplatinum and vincristine in case non-surgical treatment was required. A total of 109 of 1,044 (10.4%) protocol patients had a genetic NF-1 trait [57 female patients; median age 5.1 years (range 1-15.4 years)]. Eighty-three patients (76%) suffered from an optic pathway tumor. Neuroimaging only allowed diagnosis in 67 patients. Histology revealed pilocytic astrocytoma WHO grade I in 38 of 42 biopsied patients. Sixty-five (60%) patients received non-surgical treatment, either chemotherapy (n = 55) or irradiation (n = 10). The overall survival rate of 96% after a median observation time of 5.25 years contrasts with an event free survival rate (EFS) of 0.24 at 5 y

ears. Progressive LGG were observed even in children older than 11 years. Chiasmatic/postchiasmatic localization was a univariate risk factor for progressive disease. In the chemotherapy group, we observed a 5-year progression-free survival (PFS) rate of 0.73. Similarly, the PFS rate in the irradiation group was 0.78. Multivariate analysis revealed surgical intervention and localization within the optic pathway as factors that increased the risk of tumor progression. In this large prospective multinational study, LGG in NF-1 patients did progress in 75% of patients. Chemotherapy yielded acceptable PFS. The biological factors determining progression remain poorly understood.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 20339274

DOI: doi.org/10.2176/nmc.50.228

Titolo: Anaplastic ganglioglioma with malignant features in both neuronal and glial components--case report.

Autori: Kawataki T., Sato E., Sato T., Kinouchi H.

Data di Pubblicazione: 2010-3-27

Abstract: A 34-year-old man presented with a case of anaplastic ganglioglioma with malignant features in both neuronal and glial components manifesting as seizure episodes over 11 months. The tumor was subtotally removed, followed by irradiation and chemotherapy. The histological diagnosis was anaplastic ganglioglioma. Atypical cells were morphologically estimated as glial and neuronal cells. Though these cells were weakly positive for synaptophysin and glial fibrillary acidic protein, the neural stem cell marker nestin was extremely expressed in both these cells. The MIB-1 index was 15%. Two months later, the tumor recurred with more pleomorphic appearance and higher cellularity with increased nestin expression level. Mitotic cells and multinucleated cells were found in the neuronal components. Cytological examination found dissemination to the leptomeningeal space. The patient died 6 months after the first surgery. This rare case of anaplastic ganglioglioma with both neuronal and glial components, which were extremely positive for nestin, showed progressive worsening of the clinical course. The expression of nestin may suggest that the origin or malignant transformation in anaplastic ganglioglioma is related to the undifferentiated neural stem cells.

Journal Title: Neurologia medico-chirurgica

PUBMED ID: 20309719

DOI: doi.org/10.1007/s11060-010-0157-1

Titolo: A prospective study of temozolomide plus thalidomide during and after radiation therapy for pediatric diffuse pontine gliomas: preliminary results of the Korean Society for Pediatric Neuro-Oncology study.

Autori: Kim CY., Kim SK., Phi JH., Lee MM., Kim IA., Kim IH., Wang KC., Jung HL., Lee MJ., Cho BK.

Data di Pubblicazione: 2010-3-24

Abstract: This prospective study was performed to determine the efficacy and safety of temozolomide (TMZ) plus thalidomide during and after radiation therapy (RT) in pediatric patients with newly diagnosed diffuse pontine glioma (DPG). Seventeen patients with pediatric DPG were enrolled between November 2004 and March 2008. The median age was eight years (range, 3-16 years); seven patients were male and ten were female. With the exception of one glioblastoma case, which was diagnosed via open biopsy, all diagnoses were established using neuroradiological studies. The authors used the Korean Society for Pediatric Neuro-Oncology (KSPNO)-A053 protocol. The mean follow-up period was 12 months (range, 8.5-25 months). Five patients were withdrawn from the study. The rates of response to treatment and survival were analyzed in 12 patients. Ten out of the 12 patients showed a partial response (PR), whereas one patient exhibited stable disease (SD) and another patient had progressive disease (PD). The tumor control rate was 92% (11/12) and the response rate was

as 83% (10/12). The median progression-free survival (PFS) of the 12 patients was 7.2 months (95% confidence interval (CI), 3.6-10.7). Six-month and twelve-month PFS were 58.3 and 16.7%, respectively. Overall survival (OS) was 12.7 months (95% CI, 10.4-15.1). One and two-year survival were 58.3 and 25%, respectively. The main adverse effect was hematological toxicity, with four patients exhibiting grade 3 or 4 toxicity. All patients tolerated the regimen well enough to continue the adjuvant chemotherapy. No *Pneumocystis jirovecii* pneumonia was noted. The TMZ plus thalidomide regimen was safe and tolerated well enough to be administered on an outpatient basis. Larger studies are required to demonstrate the efficacy of this regimen.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 20238235

DOI: doi.org/10.1007/s11060-010-0141-9

Titolo: The addition of high-dose tamoxifen to standard radiotherapy does not improve the survival of patients with diffuse intrinsic pontine glioma.

Autori: Michalski A., Bouffet E., Taylor RE., Hargrave D., Walker D., Picton S., Robinson K., Pizer B., Bujkiewicz S.

Data di Pubblicazione: 2010-3-19

Abstract: The study aimed to examine the tolerability of the combination of radiotherapy and tamoxifen and the effect on median and event free survival as well as collecting data on the use of steroids in this population. 31 patients with diffuse intrinsic pontine glioma, diagnosed on clinical and radiological criteria, were treated with high-dose oral tamoxifen (120 mg/m<sup>2</sup>/day) given concomitantly with standard dose radiotherapy (54 Gy in 1.8 Gy fractions over 6 weeks). Results Tamoxifen was well tolerated with no grade 3 or 4 CTC toxicity reported. At 1 year, the progression free and event free survival were 3.2% (95% CI: 0.2-14.1%), and at 6 months 19.4% (CI: 7.9% to 34.6%). The overall survival at 1 year was 16.1% (CI: 5.9-30.9%) with median survival 6.32 months. In this study, in which tamoxifen was used in conjunction with radiotherapy, progression free survival was shown to be less good when compared with historical data HR = 3.1 (CI: 1.7-5.7). There was no significant reduction in overall survival. The addition of high-dose tamoxifen, although well tolerated, confers no clinical benefit to patients treated with diffuse intrinsic pontine glioma treated with standard radiotherapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 20217098

DOI: doi.org/10.1007/s00381-010-1106-1

Titolo: Role of temozolomide in the treatment of newly diagnosed diffuse brainstem glioma in children: experience at a single institution.

Autori: Chiang KL., Chang KP., Lee YY., Huang PI., Hsu TR., Chen YW., Chang FC., Wong TT.

Data di Pubblicazione: 2010-3-11

Abstract: In this study, CCRT with TMZ followed by adjuvant TMZ did not result in a better outcome when compared with RT alone followed by adjuvant TMZ. In addition, TMZ either as adjuvant therapy or as CCRT did not improve the prognosis of the patients with newly diagnosed diffuse brainstem glioma.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 20177703

DOI: doi.org/10.1007/s00432-010-0827-6

Titolo: Long-term adjuvant administration of temozolomide in patients with glioblastoma multiforme: experience of a single institution.

Autori: Seiz M., Krafft U., Freyschlag CF., Weiss C., Schmieder K., Lohr F., Wenz F., Thomé C., Tuettenberg J.

Data di Pubblicazione: 2010-2-24

Abstract: This data set suggests that long-term administration of temozolomide is safe and efficacious. Side effects occur more frequently in the early phase of drug administration (<6 cycles). There is a strong correlation of long-term temozolomide on PFS and OS regardless of the extent of surgery and other factors.

Journal Title: Journal of cancer research and clinical oncology

PUBMED ID: 20158881

DOI: doi.org/10.1186/bcr2479

Titolo: Survival and self-renewing capacity of breast cancer initiating cells during fractionated radiation treatment.

Autori: Lagadec C., Vlashi E., Della Donna L., Meng Y., Dekmezian C., Kim K., Pajonk F.

Data di Pubblicazione: 2010-2-18

Abstract: The breast CIC population retains increased self-renewal capacity over several generations and therefore, we conclude that increases in the number of CICs after sublethal doses of radiation have potential clinical importance. Prevention of this process may lead to improved clinical outcome.

Journal Title: Breast cancer research : BCR

PUBMED ID: 20151174

DOI: doi.org/10.1007/s11060-010-0136-6

Titolo: A lower-dose, lower-toxicity cisplatin-etoposide regimen for childhood progressive low-grade glioma.

Autori: Massimino M., Spreafico F., Riva D., Biassoni V., Poggi G., Solero C., Gandola L., Genitori L., Modena P., Simonetti F., Potepan P., Casanova M., Meazza C., Clerici CA., Catania S., Sardi I., Giangaspero F.

Data di Pubblicazione: 2010-2-13

Abstract: After successfully using cisplatin (30 mg/m<sup>2</sup>/day) and etoposide (150 mg/m<sup>2</sup>/day) in ten three-day courses for progressive low-grade gliomas, a subsequent protocol reduced the daily doses of cisplatin (to 25 mg) and etoposide (to 100 mg), with the objective of achieving the same response and three-year PFS rates with lower neurotoxicity and myelotoxicity. We treated 37 patients (median age 6 years); 23 had optochiasmatic tumours and nine were metastatic cases. Diagnoses were clinical in 13 cases and histological in 24, and comprised: pilocytic astrocytoma (17), ganglioglioma (3), pilomyxoid astrocytoma (2), and fibrillary astrocytoma (2). Treatment was prompted by radiological evidence of progression and/or clinical deterioration a median 18 months after the first diagnosis. After initial MRI staging, neurological and clinical examinations were performed before each chemotherapy cycle, with MRI after the first three courses and every three months thereafter. After a median 48 months, a volume reduction was appreciable in 24 cases (65%) and response was maximum 12 months after starting treatment. The three-year EFS and OS rates were 65 and 97%, respectively. Clinical, neurological, or functional improvements were seen in 26/37 cases. No children had a WBC nadir below 2,000/mm<sup>3</sup>. Audiological toxicity caused damage in 4/34 cases. The previous protocol had achieved volume reductions in 70% of cases, causing audiological damage (data updated) in 11/31 (P = 0.023), with three-year PFS and OS rates of 70 and 100%, respectively. Lower doses of cisplatin/etoposide are still effective in progressive low-grade glioma, with less acute and persistent morbidity.

Journal Title: Journal of neuro-oncology

PUBMED ID: 20142599

DOI: doi.org/10.1200/JCO.2009.23.5952

Titolo: Universal poor survival in children with medulloblastoma harboring somatic TP53 mutations.

Autori: Tabori U., Baskin B., Shago M., Alon N., Taylor MD., Ray PN., Bouffet E., Malkin D., Hawkins C.

Data di Pubblicazione: 2010-2-10

Abstract: Lack of long-term survival in TP53-mutated medulloblastomas highlights the role of TP53 mutations in medulloblastoma resistance to conventional therapies and the need for alternative treatments, and prospective validation of these findings is needed.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 20122270

DOI: doi.org/10.1186/1471-2407-10-30

Titolo: BCNU for recurrent glioblastoma multiforme: efficacy, toxicity and prognostic factors.

Autori: Reithmeier T., Graf E., Piroth T., Trippel M., Pinsker MO., Nikkhah G.

Data di Pubblicazione: 2010-2-4

Abstract: In summary, BCNU treatment appears to be a valuable therapeutic option for recurrent glioblastomas, where no other validated radio- and/or chemotherapy are available.

Journal Title: BMC cancer

PUBMED ID: 20063115

DOI: doi.org/10.1007/s11060-009-0103-2

Titolo: Phase II NCCTG trial of RT + irinotecan and adjuvant BCNU plus irinotecan for newly diagnosed GBM.

Autori: Jaeckle KA., Ballman KV., Giannini C., Schomberg PJ., Ames MM., Reid JM., McGovern RM., Safgren SL., Galanis E., Uhm JH., Brown PD., Hammack JE., Arusell R., Nikcevich DA., Morton RF., Wender DB., Buckner JC.

Data di Pubblicazione: 2010-1-12

Abstract: Irinotecan has radiosensitizing effects and shows synergism with nitrosoureas. We performed a Phase II study of RT and irinotecan, followed by BCNU plus irinotecan in newly-diagnosed GBM. The MTD for patients receiving enzyme-inducing anticonvulsants (EIAC) was as follows: irinotecan 400 mg/m<sup>2</sup>/week on Days 1, 8, 22 and 29 during RT, followed by BCNU 100 mg/m<sup>2</sup> Day 1, and irinotecan, 400 mg/m<sup>2</sup> on Days 1, 8, 22 and 29, every 6 weeks. The MTD for non-EIAC patients was as follows: irinotecan 125 mg/m<sup>2</sup>/week on Days 1, 8, 22 and 29 during RT, followed by BCNU 100 mg/m<sup>2</sup> Day 1 and irinotecan 75 mg/m<sup>2</sup> Days 1, 8, 22 and 29, every 6 weeks. Median OS was 10.8 mos. (95% CI: 7.7-14.9); OS at 12 months was 44.6% (95% CI: 33.3-59.8) and PFS 6 was 28.6% (95% CI: 18.9-43.2). Patients went off treatment due to adverse events (7%), refusal (11%), progressive disease (48%), death (9%), and other (9%); 16% completed protocol treatment. Survival was similar in patients with variant (6/7 or 7/7) and wild-type (6/6) UGT1A1\*28 genotypic alleles. Grade 3-4 toxicity was more common in non-EIAC patients with variant alleles. SN-38 C<sub>max</sub> and AUC in EIAC patients receiving 400 mg/m<sup>2</sup> irinotecan were 20.9 ng/ml and 212 ng/ml h, and in non-EIAC patients receiving 125 mg/m<sup>2</sup>, 15.5 ng/ml and 207 ng/ml h. SN-38 AUC varied by UGT1A1\*28 status in non-EIAC patients. This regimen was not significantly active and radiosensitization was not observed. Non-EIAC patients with UGT1A1\*28 variant alleles appear particularly sensitive to toxicity from irinotecan.

Journal Title: Journal of neuro-oncology

PUBMED ID: 23226044

DOI: doi.org/10.2147/pgpm.s7940

Titolo: Update and developments in the treatment of glioblastoma multiforme - focus on bevacizumab.

Autori: Wagle N., Nghiemphu L., Lai A., Pope W., Mischel PS., Cloughesy T.

Data di Pubblicazione: 2012-12-11

Abstract: Glioblastoma is the most common primary brain tumor with a relatively poor prognosis. This article reviews the current standard therapy and discusses new developments in treatment of this disease. Surgical resection followed by radiation and chemotherapy has proven to be the most effective initial therapy. Recent advancement in molecular targeted therapies has led to the Food and Drug Administration (FDA) approval of bevacizumab in the setting of recurrent glioblastoma. The molecular pathways of glioblastoma growth are highlighted in this review. While numerous molecular targets are currently being intensely investigated, vascular endothelial growth factor (VEGF) receptor targeted therapy has been the only one to have shown clinical effect. The role of bevacizumab in this context provides a dynamic breakthrough in cancer therapy. Clinical trials have demonstrated significantly increased overall survival and six month progression free survival (PFS) in recurrent glioblastoma treated with bevacizumab alone or in combination with irinotecan. The use of this agent has also dramatically changed the imaging characteristics of glioblastoma. The anti-angiogenesis effects of bevacizumab have complicated the criterion for determining tumor growth. This may lead to redefinition of progressive disease based on non-invasive monitoring.

Journal Title: Pharmacogenomics and personalized medicine

PUBMED ID: 20039045

DOI: doi.org/10.1007/s00381-009-1067-4

Titolo: Treatment and outcome of children with relapsed ependymoma: a multi-institutional retrospective analysis.

Autori: Zacharoulis S., Ashley S., Moreno L., Gentet JC., Massimino M., Frappaz D.

Data di Pubblicazione: 2009-12-30

Abstract: Relapsed ependymoma carries a very poor prognosis with an indolent chronic course, leading to death in approximately 90% of the patients. Complete surgical resection whenever possible should be encouraged. Radiation therapy of the relapsed lesions can provide some minor benefit whereas chemotherapy despite the occasional responses provides no benefit in the final outcome which is dismal. Efforts have to be orchestrated internationally to enroll these patients on clinical trials using biology-based therapies.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 20033471

DOI: doi.org/10.1007/s11060-009-0093-0

Titolo: Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsed high-grade gliomas: phase I clinical results.

Autori: Wismeth C., Dudel C., Pascher C., Ramm P., Pietsch T., Hirschmann B., Reinert C., Proescholdt M., Rümmele P., Schuierer G., Bogdahn U., Hau P.

Data di Pubblicazione: 2009-12-25

Abstract: Non-invasive loco-regional electro-hyperthermia (EHT) plus alkylating chemotherapy is occasionally used as salvage treatment in the relapse of patients with high-grade gliomas. Experimental data and retrospective studies suggest potential effects. However, no prospective clinical results are available. We performed a single-center prospective non-controlled single-arm Phase I trial. Main inclusion criteria were recurrent high-grade glioma WHO Grade III or IV, age 18-70, and Karnofsky performance score  $\geq$  70. Primary endpoints were dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) with the combined regimen. Groups of 3 or 4 patients were treated 2-5 times a week in a dose-escalation scheme with EHT. Alkylating chemotherapy (

ACNU, nimustin) was administered at a dose of 90 mg/m<sup>2</sup> on day 1 of 42 days for up to six cycles or until tumor progression (PD) or DLT occurred. Fifteen patients with high-grade gliomas were included. Relevant toxicities were local pain and increased focal neurological signs or intracranial pressure. No DLT occurred. In some patients, the administration of mannitol during EHT or long-term use of corticosteroids was necessary to resolve symptoms. Although some patients showed responses in their primarily treated sites, the pattern of response was not well defined. EHT plus alkylating chemotherapy is tolerable in patients with relapse of high-grade gliomas. Episodes of intracranial pressure were, at least, possibly attributed to EHT but did not cause DLTs. A Phase II trial targeting treatment effects is warranted on the basis of the results raised in this trial.

Journal Title: Journal of neuro-oncology

PUBMED ID: 19998470

DOI: doi.org/10.1002/pbc.22347

Titolo: Thiotepa/topotecan/carboplatin with autologous stem cell rescue in recurrent/refractory/poor prognosis pediatric malignancies of the central nervous system.

Autori: Gilheeney SW., Khakoo Y., Souweidane M., Wolden S., Boulad F., Dunkel IJ.

Data di Pubblicazione: 2009-12-10

Abstract: Thiotepa/topotecan/carboplatin may help consolidate remission of poor prognosis pediatric central nervous system tumors. Diagnosis and extent of disease prior to stem cell rescue may have an impact on outcome.

Journal Title: Pediatric blood & cancer

PUBMED ID: 19956971

DOI: doi.org/10.1007/s00432-009-0741-y

Titolo: Controversies concerning the application of brachytherapy in central nervous system tumors.

Autori: Liu BL., Cheng JX., Zhang X., Zhang W.

Data di Pubblicazione: 2009-12-4

Abstract: Though it is inconvincible to argue for the routine use of BRT, BRT may provide a choice for patients with large recurrent or inoperable deep-seated tumors, especially with the GliA-site technique. Radiotherapies including BRT may hold more promise if biologic mechanisms of radiation could be better understood and biologic modifications could be added in clinical trials.

Journal Title: Journal of cancer research and clinical oncology

PUBMED ID: 19951140

DOI: doi.org/10.1586/ern.09.116

Titolo: Molecularly targeted therapies for malignant glioma: rationale for combinatorial strategies.

Autori: Thaker NG., Pollack IF.

Data di Pubblicazione: 2009-12-3

Abstract: Median survival of patients with malignant glioma (MG) from time of diagnosis is approximately 1 year, despite surgery, irradiation and conventional chemotherapy. Improving patient outcome relies on our ability to develop more effective therapies that are directed against the unique molecular aberrations within a patient's tumor. Such molecularly targeted therapies may provide novel treatments that are more effective than conventional chemotherapeutics. Recently developed therapeutic strategies have focused on targeting several core glioma signaling pathways, including pathways mediated by growth-factors, PI3K/Akt/PTEN/mTOR, Ras/Raf/MEK/MAPK and other vital pathways. However, given the molecular diversity, heterogeneity and diverging and co

Converging signaling pathways associated with MG, it is unlikely that any single agent will have efficacy in more than a subset of tumors. Overcoming these therapeutic barriers will require multiple agents that can simultaneously inhibit these processes, providing a rationale for combination therapies. This review summarizes the currently implemented single-agent and combination molecularly targeted therapies for MG.

Journal Title: Expert review of neurotherapeutics

PUBMED ID: 19951061

DOI: doi.org/10.3171/2009.9.FOCUS09187

Titolo: Role of stereotactic radiosurgery and fractionated stereotactic radiotherapy for the treatment of recurrent glioblastoma multiforme.

Autori: Romanelli P., Conti A., Pontoriero A., Ricciardi GK., Tomasello F., De Renzis C., Innocenzi G., Esposito V., Cantore G.

Data di Pubblicazione: 2009-12-3

Abstract: Glioblastoma multiforme (GBM) is a devastating malignant brain tumor characterized by resistance to available therapeutic approaches and relentless malignant progression that includes widespread intracranial invasion, destruction of normal brain tissue, progressive disability, and death. Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (fSRT) are increasingly used in patients with recurrent GBM to complement traditional treatments such as resection, conventional external beam radiotherapy, and chemotherapy. Both SRS and fSRT are powerful noninvasive therapeutic modalities well suited to treat focal neoplastic lesions through the delivery of precise, high-dose radiation. Although no randomized clinical trials have been performed, a variety of retrospective studies have been focused on the use of SRS and fSRT for recurrent GBMs. In addition, state-of-the-art neuroimaging techniques, such as MR spectroscopic imaging, diffusion tensor tractography, and nuclear medicine imaging, have enhanced treatment planning methods leading to potentially improved clinical outcomes. In this paper the authors reviewed the current applications and efficacy of SRS and fSRT in the treatment of GBM, highlighting the value of these therapies for recurrent focal disease.

Journal Title: Neurosurgical focus

PUBMED ID: 19945857

DOI: doi.org/10.1016/j.ejca.2009.10.029

Titolo: EORTC study 26041-22041: phase I/II study on concomitant and adjuvant temozolomide (TMZ) and radiotherapy (RT) with PTK787/ZK222584 (PTK/ZK) in newly diagnosed glioblastoma.

Autori: Brandes AA., Stupp R., Hau P., Lacombe D., Gorlia T., Tosoni A., Mirimanoff RO., Kros JM., van den Bent MJ.

Data di Pubblicazione: 2009-12-1

Abstract: In our phase I study once daily administration of up to 1000 mg of PTK/ZK in conjunction with concomitant temozolomide and radiotherapy was feasible and safe. Prolonged administration of this oral agent is manageable. The planned randomised phase II trial was discontinued right at its onset due to industry decision not to further develop this agent.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 19944967

DOI: doi.org/10.1016/j.nec.2009.08.010

Titolo: Passive antibody-mediated immunotherapy for the treatment of malignant gliomas.

Autori: Mitra S., Li G., Harsh GR.

Data di Pubblicazione: 2009-12-1



Abstract: Despite advances in understanding the molecular mechanisms of brain cancer, the outcome of patients with malignant gliomas treated according to the current standard of care remains poor. Novel therapies are needed, and immunotherapy has emerged with great promise. The diffuse infiltration of malignant gliomas is a major challenge to effective treatment; immunotherapy has the advantage of accessing the entire brain with specificity for tumor cells. Therapeutic immune approaches include cytokine therapy, passive immunotherapy, and active immunotherapy. Cytokine therapy involves the administration of immunomodulatory cytokines to activate the immune system. Active immunotherapy is the generation or augmentation of an immune response, typically by vaccination against tumor antigens. Passive immunotherapy connotes either adoptive therapy, in which tumor-specific immune cells are expanded ex vivo and reintroduced into the patient, or passive antibody-mediated therapy. In this article, the authors discuss the preclinical and clinical studies that have used passive antibody-mediated immunotherapy, otherwise known as serotherapy, for the treatment of malignant gliomas.

Journal Title: Neurosurgery clinics of North America

PUBMED ID: 19940404

DOI: doi.org/10.2176/nmc.49.532

Titolo: Glioblastoma multiforme associated with klinefelter syndrome.

Autori: Sasayama T., Mizukawa K., Sakagami Y., Mizowaki T., Tanaka K., Ohbayashi C., Mori K., Kitazawa S., Kohmura E.

Data di Pubblicazione: 2009-11-27

Abstract: A 54-year-old man with Klinefelter syndrome presented with glioblastoma multiforme manifesting as a 2-week history of motor weakness of the bilateral extremities. Magnetic resonance imaging showed multiple heterogeneously enhanced tumors in the bilateral frontal lobes. Angiography showed no tumor stain or arteriovenous shunt. The tumor was partially removed through a right craniotomy. The histological diagnosis was glioblastoma. Immunohistochemical examination showed no O(6)-methylguanine-deoxyribonucleic acid methyltransferase protein expression. Postoperative local radiotherapy (60 Gy/30 fractions) combined with temozolomide (75 mg/m<sup>2</sup> x 42 days) and interferon-beta (3,000,000 U, 3 times/week) was performed. The patient's clinical status rapidly deteriorated during chemoradiotherapy, and he died of tumor progression 3.5 months after the surgery. Postmortem examination revealed widespread glioblastoma infiltrating the basal ganglia and thalamus. Klinefelter syndrome is associated with increased cancer predisposition, especially for male breast cancer and germ cell tumors, but glioma is extremely rare. The abnormal genetic constitution of this patient may have been directly responsible for the poor outcome.

Journal Title: Neurologia medico-chirurgica

PUBMED ID: 19933982

DOI: doi.org/10.1212/WNL.0b013e3181c34ace

Titolo: IDH1 mutations in low-grade astrocytomas predict survival but not response to temozolomide.

Autori: Dubbink HJ., Taal W., van Marion R., Kros JM., van Heuvel I., Bromberg JE., Zonnenberg BA., Zonnenberg CB., Postma TJ., Gijtenbeek JM., Boogerd W., Groenendijk FH., Smitt PA., Dinjens WN., van den Bent MJ.

Data di Pubblicazione: 2009-11-26

Abstract: These results indicate that IDH1 mutations identify a subgroup of gliomas with an improved survival, but are unrelated to the temozolomide response.

Journal Title: Neurology

PUBMED ID: 19829279

DOI: doi.org/10.1097/BRS.0b013e3181b95c6f

Titolo: Primary intramedullary tumors of the spinal cord.

Autori: Harrop JS., Ganju A., Groff M., Bilsky M.

Data di Pubblicazione: 2009-10-16

Abstract: The most important factor in determining the IMSCT patient's long-term neurologic and functional outcome after surgery is the patient's preoperative neurologic status. However, this must be taken in the context of the underlying tumor histology. Therefore, resection is reserved for progressive neurologic decline and serial monitoring for asymptomatic individuals. Adjuvant therapy is an option for high grade astrocytomas (WHO grades 3-4).

Journal Title: Spine

PUBMED ID: 19904263

DOI: doi.org/10.1038/sj.bjc.6605411

Titolo: Multicentre phase II studies evaluating imatinib plus hydroxyurea in patients with progressive glioblastoma.

Autori: Reardon DA., Dresemann G., Taillibert S., Campone M., van den Bent M., Clement P., Blomquist E., Gordower L., Schultz H., Raizer J., Hau P., Easaw J., Gil M., Tonn J., Gijtenbeek A., Schlegel U., Bergstrom P., Green S., Weir A., Nikolova Z.

Data di Pubblicazione: 2009-11-12

Abstract: Imatinib in addition to hydroxyurea was well tolerated among patients with recurrent GBM but did not show clinically meaningful anti-tumour activity.

Journal Title: British journal of cancer

PUBMED ID: 19859666

DOI: doi.org/10.1007/s11060-009-9981-6

Titolo: Imaging response criteria for recurrent gliomas treated with bevacizumab: role of diffusion weighted imaging as an imaging biomarker.

Autori: Jain R., Scarpace LM., Ellika S., Torcuator R., Schultz LR., Hearn D., Mikkelsen T.

Data di Pubblicazione: 2009-10-28

Abstract: The purpose of this study was to assess the usefulness of diffusion weighted imaging as an additional imaging biomarker for treatment response in recurrent/progressive malignant gliomas treated with bevacizumab alone or in combination with other chemotherapeutic agents. Twenty patients treated with bevacizumab alone or concurrent chemotherapy were followed up with serial MR imaging. Volume and ADC values of contrast enhancing lesion (CEL(vol), CEL(ADC)) and also of non-enhancing lesion (NEL(vol), NEL(ADC)) were obtained. CEL(vol) showed a progressive decrease in non-progressors with a median percentage change of -73.2% (P = 0.001) as compared to -33.4% for progressors by 1 year/last imaging (P = 0.382). NEL(vol) also showed a decrease in non-progressors on follow up imaging though only significant for 3 months follow up (P = 0.042). In progressors, CEL(vol) and NEL(vol) showed initial decrease followed by slight increase by 1 year/last imaging though not significant (P value of 0.382 and 0.46, respectively). CEL(ADC) and NEL(ADC) in non-progressors did not show any statistically significant change though there was a slight trend for positive percent change especially for CEL(ADC) by 1 year/last imaging follow up study (P value of 0.077 and 0.339, respectively). Progressors showed a progressive negative percent change of CEL(ADC) and NEL(ADC). In progressors, NEL(ADC) decreased at 6 weeks (P = 0.054), 3 months (P = 0.023) and 1 year/last (P = 0.078) as compared to baseline study and was also statistically significant as compared to non-progressors at 6 weeks (P = 0.047) and 3 months (P = 0.025). CEL(ADC) and NEL(ADC) appear to follow different trends over time for non-progressors and progressors with a stable to slightly progressive increase in non-progressors and a progressive decrease in

progressors, especially early on. These findings suggest that DWI may be used as an additional imaging biomarker for early treatment response.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 19857784  
DOI: doi.org/10.1016/j.ijrobp.2008.12.032  
Titolo: Bevacizumab as therapy for radiation necrosis in four children with pontine gliomas.  
Autori: Liu AK., Macy ME., Foreman NK.  
Data di Pubblicazione: 2009-10-28  
Abstract: In children with pontine gliomas, bevacizumab may provide both the therapeutic benefit and diagnostic information. More formal evaluation of bevacizumab in these children is needed.  
Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 19856394  
DOI: doi.org/10.1002/pbc.22323  
Titolo: MGMT as a potential stratification marker in relapsed high-grade glioma of children: the HIT-GBM experience.  
Autori: Schlosser S., Wagner S., Mühlisch J., Hasselblatt M., Gerss J., Wolf JE., Frühwald MC.  
Data di Pubblicazione: 2009-10-27  
Abstract: DNA methylation, but not protein expression of MGMT was associated with an increased median EFS and OS of children with relapsed HGG. MGMT methylation status warrants prospective evaluation as a stratification marker for children with HGG.  
Journal Title: Pediatric blood & cancer

PUBMED ID: 19852061  
DOI: doi.org/10.1002/pbc.22319  
Titolo: Adjuvant dendritic cell-based tumour vaccination for children with malignant brain tumours.  
Autori: Ardon H., De Vleeschouwer S., Van Calenbergh F., Claes L., Kramm CM., Rutkowski S., Wolff JE., Van Gool SW.  
Data di Pubblicazione: 2009-10-24  
Abstract: In this exploratory study, HGG and ATRT seem to respond more favourably to vaccination than MB/PNET and ependymoma. Although preliminary, our results are promising and support further testing of DC-based immunotherapy in new treatment protocols for HGG and ATRT.  
Journal Title: Pediatric blood & cancer

PUBMED ID: 19847765  
DOI: Mancante  
Titolo: Gliosarcoma with chondroblastic osteosarcomatous differentiation: report of two cases with clinicopathologic and immunohistochemical features.  
Autori: Barut F., Kandemir NO., Ozdamar SO., Gul S., Bektas S., Gun BD., Bahadir B.  
Data di Pubblicazione: 2009-10-23  
Abstract: Gliosarcoma is a rare tumor of the central nervous system characterized by a biphasic histological pattern. Our objective is to describe clinical, morphological and immunohistochemical features of two cases of gliosarcoma with chondroblastic osteosarcomatous differentiation and to discuss its pathogenetic mechanisms. CASE 1: A 52-year-old male patient underwent parietal craniotomy due to anaplastic ependymoma. The case had radiotherapy and chemotherapy postoperatively. After the first operation, additional resections were performed for tumor because of recurrences at the fourth, seventh and

tenth months. The patient died after the last tumor resection. Histopathologic examination of the postmortem biopsy revealed neoplasm displaying a biphasic morphologic pattern including both gliomatous and sarcomatous components. CASE 2: The case was a 69-year-old male patient with a right frontal lobe mass histologically diagnosed as gliosarcoma displaying sarcomatous and glial components. Immunohistochemical features were similar to those of the first case in general, but diffuse nuclear reaction with p53 protein was detected in both components. We report two cases with an extremely rare histopathological diagnosis of "gliosarcoma with features of chondroblastic osteosarcoma".

Journal Title: Turkish neurosurgery

PUBMED ID: 19840379

DOI: doi.org/10.1186/1471-2407-9-372

Titolo: Early termination of ISRCTN45828668, a phase 1/2 prospective, randomized study of sulfasalazine for the treatment of progressing malignant gliomas in adults.

Autori: Robe PA., Martin DH., Nguyen-Khac MT., Artesi M., Deprez M., Albert A., Vanbelle S., Califice S., Bredel M., Bours V.

Data di Pubblicazione: 2009-10-21

Abstract: Current Controlled Trials ISRCTN45828668.

Journal Title: BMC cancer

PUBMED ID: 19836372

DOI: doi.org/10.1016/j.ejphar.2009.10.010

Titolo: EGF receptor inhibitors in the treatment of glioblastoma multiform: old clinical allies and newly emerging therapeutic concepts.

Autori: Gadji M., Crous AM., Fortin D., Krcek J., Torchia M., Mai S., Drouin R., Klonisch T.

Data di Pubblicazione: 2009-10-20

Abstract: Glioblastoma multiform (GBM) is the most common malignant brain tumour in adults. Despite decades of experimentation to improve the outcome of patients with GBM this highly aggressive tumour remains fatal. Primary GBM are often characterized by the over-expression of epidermal growth factor (EGF) receptor/HER1 and/or its mutational variants, with ligand-independent, constitutively active EGF receptor VIII variant most frequently observed in GBM. EGF receptor signalling can promote tumorigenesis by increasing cell proliferation, tissue invasion, neoangiogenesis, tumour cell chemoresistance, and by inhibiting apoptosis of cancer cells. EGF receptor was the first receptor to serve as target for cancer therapy of many solid tumours. After 2 decades of intensive targeting of EGF receptor for molecular therapy, several anti-EGF receptor inhibitors are now available in the clinic. Therapeutic strategies to target EGF receptor and EGF receptor mutant forms in GBM include humanized monoclonal antibodies, tyrosine kinase inhibitors, and RNAi compounds. However, despite the fact that most EGF receptor-directed glioma therapies to date have focused on single therapeutic agents, a multi-directional approach involving targeted inhibition of multiple signalling pathways has emerged as a more robust therapeutical approach. Furthermore, the emergence of the hypothesis of "brain cancer stem cells" in the bulb of GBM identifies this population of cells with self-renewal capacity as novel obligatory targets for efficient cure of GBM. Here we summarize current findings on the clinical role of these EGF receptor inhibitory therapeutic agents in the treatment of GBM.

Journal Title: European journal of pharmacology

PUBMED ID: 19822869

DOI: doi.org/10.1212/WNL.0b013e3181bc0184

Titolo: Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma.

Autori: Iwamoto FM., Abrey LE., Beal K., Gutin PH., Rosenblum MK., Reuter VE., DeAngelis LM., Lassman AB.

Data di Pubblicazione: 2009-10-14

Abstract: Contrast enhanced MRI does not adequately assess disease status during bevacizumab therapy for recurrent glioblastoma (GBM). A nonenhancing tumor pattern of progression is common after treatment with bevacizumab for GBM and is correlated with worse survival. Treatments after bevacizumab failure provide only transient tumor control.

Journal Title: Neurology

PUBMED ID: 19751941

DOI: doi.org/10.1016/j.jns.2009.08.047

Titolo: Primary leptomeningeal anaplastic oligodendroglioma with a 1p36-19q13 deletion: report of a unique case successfully treated with Temozolomide.

Autori: Michotte A., Chaskis C., Sadones J., Veld PI., Neyns B.

Data di Pubblicazione: 2009-9-16

Abstract: Primary leptomeningeal oligodendroglioma occurs very rarely and in only one patient a deletion of chromosome 1p has been reported. We describe a 60-year-old man with a prior history of an epileptic seizure three years earlier, who was referred because of depression and a rapid evolving cognitive impairment. Brain MRI showed a diffuse right parieto-occipital subarachnoid enhancing lesion without intra-axial extension. The diagnosis of an anaplastic oligodendroglioma (WHO grade 3) was made on pathological examination. Molecular analysis using the FISH technique revealed a combined deletion of chromosomes 1p36 and 19q13. A rapid progression of the lesion was shown on MRI with leptomeningeal spinal metastases. The patient was treated with Temozolomide (TMZ) 150 mg/m<sup>2</sup> for 5 days every 4 weeks and showed a marked clinical recovery. Serial MRI disclosed a near complete regression of the lesions with no residual enhancement left after 6 cycles of chemotherapy. At progression following 8 cycles of TMZ the patient underwent craniospinal radiotherapy with complete response of his disease. To our knowledge this is the first report of a patient with a primary leptomeningeal anaplastic oligodendroglioma with diffuse spinal seeding bearing a 1p36/19q13 deletion. Our patient achieved a durable clinical and radiological remission following TMZ treatment. Molecular analysis with determination of chromosome 1p/19q deletions should be performed in all cases of leptomeningeal gliomas to select those patients who might benefit from TMZ chemotherapy.

Journal Title: Journal of the neurological sciences

PUBMED ID: 19737359

DOI: doi.org/10.1111/j.1440-1789.2009.01051.x

Titolo: B-cell dominant lymphocytic primary angiitis of the central nervous system: four biopsy-proven cases.

Autori: Myung J., Kim B., Yoon BW., Lee SK., Sung JJ., Chung CK., Chang KH., Park SH.

Data di Pubblicazione: 2009-9-10

Abstract: We report four cases of biopsy-proven B-cell-rich primary angiitis of the central nervous system (PACNS). The mean age of the patients was 29 years (range, 23-37 years). The patients suffered from unilateral weakness (n = 2), seizure (n = 1), and hypersomnia, anorexia and confusion (n = 1). The vital signs and the results of laboratory tests were within normal limits in all the four cases except erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). ESR was elevated in one patient and CRP was elevated in two patients. The magnetic resonance imaging (MRI) scans revealed single (n = 2) or multiple (n = 2) irregularly enhancing lesions. Radiological studies initially indicated tumors such as glioma (n = 2) or lymphoma (n = 1), except in

one case, in which the radiological analysis indicated vasculitis or demyelinating disease. All the cases involved both medium-sized (50-250 microm in diameter) and small-sized vessels (20-49 microm in diameter). The vascular, perivascular and parenchymal lymphocytes were polymorphous; however, CD20-positive B-cells were predominated in blood vessels while the CD8-positive T-cells infiltrated predominantly in brain parenchyma. Therefore, our patients revealed B-cell dominant lymphocytic vasculitis. Two patients who underwent active treatment (corticosteroid alone or with cyclophosphamide) showed remarkable clinical and radiological improvement but two patients still have initial neurological symptoms, namely, confusion and newly developed seizures, respectively, during the 19-101-month follow-up periods; this effect can be attributed to irreversible brain damage. Therefore, although early brain biopsy may be associated with histopathologic diagnostic pitfalls, it is a mandatory procedure for obtaining a confirmative diagnosis as well initiating early therapy, thereby reducing brain damage.

Journal Title: Neuropathology : official journal of the Japanese Society of Neuropathology

PUBMED ID: 19724855

DOI: doi.org/10.3892/or\_00000499

Titolo: Promoter methylation and expression analysis of MGMT in advanced pediatric brain tumors.

Autori: Sardi I., Cetica V., Massimino M., Buccoliero AM., Giunti L., Genitori L., Aricò M.

Data di Pubblicazione: 2009-9-3

Abstract: Insufficient response to oral temozolomide (TMZ) in children with brain tumor may depend on the repair-action of inducible O6-methylguanine-DNA methyltransferase (MGMT). To investigate the clinical relevance of MGMT expression, we analyzed MGMT levels by qRT-PCR and immunohistochemistry, and the methylation of gene promoter in patients with relapsed or refractory brain tumor, enrolled in an off-label trial with oral temozolomide. The drug was administered at the dose of 200 mg/m<sup>2</sup>/day in patients with no prior cranio-spinal irradiation, and 180 mg/m<sup>2</sup>/day in those with previous radiotherapy and/or high-dose chemotherapy followed by autologous hematopoietic stem cell rescue. Nine patients with recurrent ependymoma (n=3), low grade glioma (n=3), glioblastoma (n=1), relapsed medulloblastoma (n=2) were enrolled in the study. Median absolute MGMT mRNA expression level standardized for GAPDH was 1.06 (range -0.453 to 3.932). The median relative expression level (RQ=2<sup>-ddC</sup>) was 4.29 (range 1.585 to 12.228). By immunohistochemistry, the score was 2+ in 6 of the 9 tumor samples, and 1+ in 3, while none was MGMT negative. Methylation of MGMT promoter was detected in only one ependymoma sample. The heterogeneous PFS in our patients treated with second line TMZ, indicates that MGMT expression alone is insufficient to predict the response to TMZ, presumably because of the DNA repair mechanisms involved.

Journal Title: Oncology reports

PUBMED ID: 19717889

DOI: doi.org/10.1088/0031-9155/54/18/012

Titolo: The quantification of dynamic FET PET imaging and correlation with the clinical outcome in patients with glioblastoma.

Autori: Thiele F., Ehmer J., Piroth MD., Eble MJ., Coenen HH., Kaiser HJ., Schaefer WM., Buell U., Boy C.

Data di Pubblicazione: 2009-9-1

Abstract: The PET tracer O-(2-[18F]Fluoroethyl)-L-tyrosine (FET) has been shown to be valuable for different roles in the management of brain tumours. The aim of this study was to evaluate several quantitative measures of dynamic FET PET imaging in patients with resected glioblastoma. We evaluated dynamic FET PET in nine patients with histologically confirmed glioblastoma. Foll

owing FET PET, all subjects had radiation and chemotherapy. Tumour ROIs were defined by a threshold-based region-growing algorithm. We compared several standard measures of tumour uptake and uptake kinetics: SUV, SUV/background, distribution volume ratio (DVR), weighted frame differences and compartment model parameters. These measures were correlated with disease-free and overall survival, and analysed for statistical significance. We found that several measures allowed robust quantification. SUV and distribution volume did not correlate with clinical outcome. Measures that are based on a background region (SUV/BG, Logan-DVR) highly correlated with disease-free survival ( $r = -0.95$ ,  $p < 0.0001$ ), but not overall survival. Some advanced measures also showed a prognostic value but no improvement over the simpler methods. We conclude that FET PET probably has a prognostic value in patients with resected glioblastoma. The ratio of SUV to background may provide a simple and valuable predictive measure of the clinical outcome. Further studies are needed to confirm these explorative results.

Journal Title: Physics in medicine and biology

PUBMED ID: 19695790

DOI: doi.org/10.1016/j.ijrobp.2009.04.058

Titolo: Incidence, risks, and sequelae of posterior fossa syndrome in pediatric medulloblastoma.

Autori: Korah MP., Esiashvili N., Mazewski CM., Hudgins RJ., Tighiouart M., Janss AJ., Schwaibold FP., Crocker IR., Curran WJ., Marcus RB.

Data di Pubblicazione: 2009-8-22

Abstract: The incidence of PFS increased in the latter study period and is proportional to more aggressive surgery. Children with midline tumors exhibiting brainstem invasion are at increased risk. With the increased incidence of PFS and the permanent morbidity in many patients, the risks and benefits of complete tumor removal in all patients need to be reexamined.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 19688297

DOI: doi.org/10.1007/s11060-009-9976-3

Titolo: Imatinib in combination with hydroxyurea versus hydroxyurea alone as oral therapy in patients with progressive pretreated glioblastoma resistant to standard dose temozolomide.

Autori: Dresemann G., Weller M., Rosenthal MA., Wedding U., Wagner W., Engel E., Heinrich B., Mayer-Steinacker R., Karup-Hansen A., Fluge O., Nowak A., Mehdorn M., Schleyer E., Krex D., Olver IN., Steinbach JP., Hosius C., Sieder C., Sorenson G., Parker R., Nikolova Z.

Data di Pubblicazione: 2009-8-19

Abstract: A randomized, multicenter, open-label, phase 3 study of patients with progressive, recurrent glioblastoma multiforme (GBM) for whom front-line therapy had failed was conducted. This study was designed to determine whether combination therapy with imatinib and hydroxyurea (HU) has superior antitumor activity compared with HU monotherapy in the treatment of recurrent GBM. The target population consisted of patients with confirmed recurrent GBM and an Eastern Cooperative Oncology Group performance status of 0-2 who had completed previous treatment comprising surgical resection, irradiation therapy, and first-line chemotherapy (preferably temozolomide (TMZ) containing regimen) and who have progressed despite treatment. If first-line chemotherapy did not contain TMZ, a second completed chemotherapy was acceptable. The primary efficacy parameter was progression-free survival (PFS). The primary comparison of combination therapy versus monotherapy for PFS was not significant (adjusted  $P = 0.56$ ). The hazard ratio (HR) (adjusted HR = 0.93) was not clinically relevant. The median PFS for the combination arm was low at 6 weeks and similar to the median PFS in the monotherapy arm (6 weeks). The 6-month PFS for the two treatment groups was very similar (5% in the combination arm

vs. 7% in the monotherapy arm). No clinically meaningful differences were found between the two treatment arms, and the primary study end point was not met. Among the patients receiving imatinib, no adverse events were reported that were either previously unknown or unexpected as a consequence of the disease.

Journal Title: Journal of neuro-oncology

PUBMED ID: 19669096

DOI: doi.org/10.1007/s11060-009-9980-7

Titolo: Extended-schedule dose-dense temozolomide in refractory gliomas.

Autori: Berrocal A., Perez Segura P., Gil M., Balaña C., Garcia Lopez J., Yaya R., Rodríguez J., Reynes G., Gallego O., Iglesias L., Iglesias L.

Data di Pubblicazione: 2009-8-12

Abstract: This multicenter phase II study conducted by the Spanish Neuro-Oncology Group evaluated the activity of an extended, dose-dense temozolomide regimen in patients with temozolomide-refractory malignant glioma. Adult patients (at least 18 years of age) with WHO grade III or IV glioma and a Karnofsky Performance Status of 60 or higher were treated with temozolomide (85 mg/m<sup>2</sup>/day) for 21 consecutive days every 28-day cycle until disease progression or unacceptable toxicity. All patients had developed progressive disease either during or less than 3 months after completing previous temozolomide treatment. Forty-seven patients were treated with a median of 2 (range, 1-13) cycles of temozolomide. Before study entry, patients had received a median of 6 cycles of temozolomide: 39 (83%) as part of initial therapy and 23 (49%) as second-line therapy. Three patients (6.4%) had a partial response with durations of 8.0, 3.5, and 3.2 months; 15 patients (31.9%) had stable disease with a median duration of 2.1 months, including 2 patients with stable disease (SD) for greater than 6 months (14 and 16 months). Median time to progression was 2 months, and median overall survival from study entry was 5.1 months. The 6-month progression-free survival rate was 16.7%. The most common hematologic toxicities were lymphopenia, thrombocytopenia, and leukopenia. Lymphopenia occurred in 83% of patients and was grade 3 in 28%, but no opportunistic infections occurred. In conclusion, this extended dose-dense schedule of temozolomide appears to have modest activity in patients refractory to previous treatment with temozolomide and is associated with manageable toxicity.

Journal Title: Journal of neuro-oncology

PUBMED ID: 19657635

DOI: doi.org/10.1007/s00247-009-1368-5

Titolo: Conventional MRI at presentation does not predict clinical response to radiation therapy in children with diffuse pontine glioma.

Autori: Liu AK., Brandon J., Foreman NK., Fenton LZ.

Data di Pubblicazione: 2009-8-7

Abstract: Conventional MRI at presentation does not predict clinical response in children with diffuse pontine glioma. Additional studies with larger numbers of patients and other imaging modalities are needed.

Journal Title: Pediatric radiology

PUBMED ID: 19647954

DOI: doi.org/10.1016/j.ijrobp.2009.04.031

Titolo: Prospective evaluation of radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma.

Autori: Jalali R., Raut N., Arora B., Gupta T., Dutta D., Munshi A., Sarin R., Kurkure P.

Data di Pubblicazione: 2009-8-4



Abstract: TMZ with RT has not yielded any improvement in the outcome of DIPG compared with RT alone. Further clinical trials should explore novel treatment modalities.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 19618121

DOI: doi.org/10.1007/s11060-009-9960-y

Titolo: Comparing neuropsychological tasks to optimize brief cognitive batteries for brain tumor clinical trials.

Autori: Lageman SK., Cerhan JH., Locke DE., Anderson SK., Wu W., Brown PD.

Data di Pubblicazione: 2009-7-21

Abstract: Neuropsychological tests are increasingly being used as outcome measures in clinical trials of brain tumor therapies. This study informs development of brief neurocognitive batteries for clinical trials by identifying cognitive tasks that detect effects on a group level in a mixed brain tumor population. This is a retrospective study of brain tumor patients who completed a standardized battery sampling multiple cognitive domains using twelve subtests with widely-used task formats (the Repeatable Battery for the Assessment of Neuropsychological Status). Sixty-eight patients with brain tumors were studied (60% high-grade glioma). Forty patients (58.8%) were impaired (>2 standard deviations below published means) on at least one subtest. A combination of four subtests (Figure Copy, Coding, List Recognition, and Story Recall) captured 90% of the impaired subgroup. These results suggest visuomotor, processing speed, and verbal memory measures may be the most important domains to assess when evaluating cognitive change in brain tumor clinical trials.

Journal Title: Journal of neuro-oncology

PUBMED ID: 19593660

DOI: doi.org/10.1007/s11060-009-9957-6

Titolo: Salvage therapy with single agent bevacizumab for recurrent glioblastoma.

Autori: Chamberlain MC., Johnston SK.

Data di Pubblicazione: 2009-7-14

Abstract: A retrospective evaluation of single agent bevacizumab in adults with recurrent glioblastoma (GBM) with an objective of determining progression free survival (PFS). There is no standard therapy for recurrent GBM after failure of alkylator-based chemotherapy. A total of 50 adults, ages 36-70 years (median 64), with recurrent GBM were treated. All patients had previously been treated with surgery, concurrent radiotherapy and temozolomide, post-radiotherapy temozolomide and in 34 patients, one salvage regimen (PCV: 21, cyclophosphamide: 13). A total of 13 patients underwent repeat surgery. Patients were treated at first or second recurrence with bevacizumab, once every 2 weeks, defined as a single cycle. Neurological evaluation was performed every 2 weeks and neuroradiographic assessment following the initial 2 cycles of bevacizumab and subsequently after every 4 cycles of bevacizumab. A total of 468 cycles of bevacizumab (median 2 cycles; range 1-30) was administered. Bevacizumab-related toxicity included fatigue (16 patients; 4 grade 3), leukopenia (9; 1 grade 3), anemia (5; 0 grade 3), hypertension (7; 1 grade 3), deep vein thrombosis (4; 1 grade 3) and wound dehiscence (2; 1 grade 3). 21 patients (42%) demonstrated a partial radiographic response and 29 (58%) progressive disease following 1-2 cycles of bevacizumab. Time to tumor progression ranged from 0.5 to 15 months (median: 1.0 months). Survival ranged from 2 to 17 months (median: 8.5 months). 6-month and 12-month PFS were 42% and 22% respectively. Single agent bevacizumab demonstrated efficacy and acceptable toxicity in this cohort of adults with recurrent alkylator-refractory GBM.

Journal Title: Journal of neuro-oncology

PUBMED ID: 19584260

DOI: doi.org/10.1158/1541-7786.MCR-08-0479

Titolo: Therapeutic inhibition of the epidermal growth factor receptor in high-grade gliomas: where do we stand?

Autori: Karpel-Massler G., Schmidt U., Unterberg A., Halatsch ME.

Data di Pubblicazione: 2009-7-9

Abstract: High-grade gliomas account for the majority of intra-axial brain tumors. Despite abundant therapeutic efforts, clinical outcome is still poor. Thus, new therapeutic approaches are intensely being investigated. Overexpression of the epidermal growth factor receptor (HER1/EGFR) is found in various epithelial tumors and represents one of the most common molecular abnormalities seen in high-grade gliomas. Dysregulated HER1/EGFR is found in 40% to 50% of glioblastoma, the most malignant subtype of glioma. Several agents such as tyrosine kinase (TK) inhibitors, antibodies, radio-immuno conjugates, ligand-toxin conjugates, or RNA-based agents have been developed to target HER1/EGFR or its mutant form, EGFRvIII. To date, most agents are in various stages of clinical development. Clinical data are sparse but most advanced for TK inhibitors. Although data from experimental studies seem promising, proof of a significant clinical benefit is still missing. Among the problems that have to be further addressed is the prediction of the individual patient's response to HER1/EGFR-targeted therapeutics based on molecular determinants. It is quite possible that blocking HER1/EGFR alone will not sufficiently translate into a clinical benefit. Therefore, a multiple target approach concomitantly aimed at different molecular sites might be a favorable concept. This review focuses on current HER1/EGFR-targeted therapeutics and their development for high-grade gliomas.

Journal Title: Molecular cancer research : MCR

PUBMED ID: 19569246

DOI: doi.org/10.1002/cncr.24524

Titolo: Temozolomide for recurrent intracranial supratentorial platinum-refractory ependymoma.

Autori: Chamberlain MC., Johnston SK.

Data di Pubblicazione: 2009-7-2

Abstract: TMZ in this dose schedule demonstrated little efficacy in a cohort of adults with recurrent, intracranial, platinum-refractory ependymoma.

Journal Title: Cancer

PUBMED ID: 19567132

DOI: Mancante

Titolo: Antiangiogenic therapy with bevacizumab in recurrent malignant gliomas: analysis of the response and core pathway aberrations.

Autori: Zhang W., Qiu XG., Chen BS., Li SW., Cui Y., Ren H., Jiang T.

Data di Pubblicazione: 2009-7-2

Abstract: Bevacizumab in combination with chemotherapeutic agents may be an effective strategy for patients with recurrent malignant glioma. Activated MAPK and AKT might be possible biomarkers for selecting suitable patients for this targeted therapy.

Journal Title: Chinese medical journal

PUBMED ID: 19557499

DOI: doi.org/10.1007/s11060-009-9946-9

Titolo: Neurological outcome of long-term glioblastoma survivors.

Autori: Hottinger AF., Yoon H., DeAngelis LM., Abrey LE.

Data di Pubblicazione: 2009-6-27

Abstract: Extended survival of 3 or more years is rare in patients with glioblastoma (GBM) but is becoming more common. Clinical outcome has not been well studied. We reviewed GBM patients at Memorial Sloan-Kettering Cancer Center between 2001 and 2003 who were seen for two or more visits. Patient characteristics and long-term clinical outcomes were reviewed for patients who had survived 3 or more years following diagnosis. Thirty-nine (11%) of 352 GBM patients were identified as long-term survivors. Median survival was 9.15 years (range: 3-18 years). Median age was 47 years (range: 16-69); 13% were 65 years or older. Median KPS was 90 (range: 50-100). One long-term survivor underwent biopsy alone; 19 patients each had either complete or subtotal resection. All received focal radiotherapy (RT) with a median dose of 5940 cGy; 18% received concurrent temozolomide. Adjuvant chemotherapy was administered to 35 (90%). Twelve patients (31%) remained in continuous remission. Twenty-seven had tumor progression a median of 29.2 months after diagnosis (range: 1.2-167 months); 18 had multiple relapses. Median KPS at last follow-up was 70 (range: 40-100); 85% of long-term survivors had at least one significant neurologic deficit. Eleven (28%) had clinically significant RT-induced leukoencephalopathy, 9 (23%) developed RT necrosis and 9 (23%) treatment-related strokes. Treatment-related complications occurred a median of 2.7 years from diagnosis (range: 0.9-11.5 years). Long-term survivors remain rare, but are found across all age groups despite multiple recurrences; clinically significant delayed complications of treatment are common.

Journal Title: Journal of neuro-oncology

PUBMED ID: 19549889

DOI: doi.org/10.1158/0008-5472.CAN-09-0814

Titolo: A "vascular normalization index" as potential mechanistic biomarker to predict survival after a single dose of cediranib in recurrent glioblastoma patients.

Autori: Sorensen AG., Batchelor TT., Zhang WT., Chen PJ., Yeo P., Wang M., Jennings D., Wen PY., Lahdenranta J., Ancukiewicz M., di Tomaso E., Duda DG., Jain RK.

Data di Pubblicazione: 2009-6-25

Abstract: Early imaging or blood biomarkers of tumor response are desperately needed to customize antiangiogenic therapy for cancer patients. Anti-vascular endothelial growth factor (VEGF) therapy can "normalize" brain tumor vasculature by decreasing vessel diameter and permeability, and thinning the abnormally thick basement membrane. We hypothesized that the extent of vascular normalization will be predictive of outcome of anti-VEGF therapy in glioblastoma. We used advanced magnetic resonance imaging methods to monitor vascular parameters and treatment response in 31 recurrent glioblastoma patients enrolled in a phase II trial of cediranib, an oral pan-VEGF receptor tyrosine kinase inhibitor. We evaluated the correlation between clinical outcome and magnetic resonance imaging-measured changes in vascular permeability/flow (i.e., K(trans)) and in microvessel volume, and the change of circulating collagen IV levels, all after a single dose of cediranib. Here, we show that evaluation of biomarkers as early as after one day of anti-VEGF therapy with cediranib is predictive of response in patients with recurrent glioblastoma. Changes in K(trans), microvessel volume, and circulating collagen IV correlated with duration of overall survival and/or progression-free survival ( $P < 0.05$ ). When we combined these three parameters into a "vascular normalization index," we found that it closely associated with overall survival ( $\rho = 0.54$ ;  $P = 0.004$ ) and progression-free survival ( $\rho = 0.6$ ;  $P = 0.001$ ). The vascular normalization index described here should be validated in randomized clinical trials.

Journal Title: Cancer research

PUBMED ID: 19536096

DOI: doi.org/10.1038/sj.bjc.6605127

Titolo: Extent of MGMT promoter methylation correlates with outcome in glioblastomas given temozolomide and radiotherapy.

Autori: Dunn J., Baborie A., Alam F., Joyce K., Moxham M., Sibson R., Crooks D., Husband D., Shenoy A., Brodbelt A., Wong H., Liloglou T., Haylock B., Walker C.

Data di Pubblicazione: 2009-6-19

Abstract: These data indicate that MGMT methylation is prognostically significant in glioblastomas given chemoradiotherapy in the routine clinic; furthermore, the extent of methylation may be used to provide additional prognostic stratification.

Journal Title: British journal of cancer

PUBMED ID: 19506143

DOI: doi.org/10.1001/archneurol.2009.74

Titolo: Occurrence of basal ganglia germ cell tumors without a mass.

Autori: Almubarak S., Gan YC., Steinbok P., Hendson G., Poskitt K., Nadel H., Goddard K., Hukin J.

Data di Pubblicazione: 2009-6-10

Abstract: Germ cell tumor should be considered in patients with an indolently progressive neurological course, particularly if basal ganglia calcification is present with or without enhancement, asymmetric brain atrophy, or a mass.

Journal Title: Archives of neurology

PUBMED ID: 19491283

DOI: doi.org/10.1093/annonc/mdp032

Titolo: Stratified phase II trial of cetuximab in patients with recurrent high-grade glioma.

Autori: Neyns B., Sadones J., Joosens E., Bouttens F., Verbeke L., Baurain J F., D'Hondt L., Strauven T., Chaskis C., In't Veld P., Michotte A., De Greve J.

Data di Pubblicazione: 2009-6-4

Abstract: Cetuximab was well tolerated but had limited activity in this patient population with progressive HGG. A minority of patients may derive a more durable benefit but were not prospectively identified by EGFR gene copy number.

Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 19485728

DOI: doi.org/10.3171/2009.2.PEDS0861

Titolo: Predictors of tumor progression among children with gangliogliomas. Clinical article.

Autori: El Khashab M., Gargan L., Margraf L., Koral K., Nejat F., Swift D., Weprin B., Bowers DC.

Data di Pubblicazione: 2009-6-3

Abstract: The PFS and overall survival of children with gangliogliomas are good. Tumors located in the cerebral hemispheres, the achievement of total resection, and seizures at presentation were associated with prolonged PFS. Cox regression analysis identified presenting symptoms including seizures as significant predictive factors of PFS. Prospective studies with larger numbers of children are needed to define the significant factors of tumor progression.

Journal Title: Journal of neurosurgery. Pediatrics

PUBMED ID: 19484244

DOI: doi.org/10.1007/s00347-009-1927-z

Titolo: [Clinical course of a solitary retinal astrocytoma].

Autori: Töteberg-Harms M., Paulsen F., Duncker G.I., Sel S.

Data di Pubblicazione: 2009-6-2

Abstract: Retinal astrocytomas are benign tumors of the retina. Their localization can be solitary, multiple, or bilateral in both eyes. It is also known that they can be part of a phakomatosis syndrome (i.e., tuberous sclerosis or neurofibromatosis). Because retinal astrocytomas have a slow growth rate, yearly controls by an ophthalmologist with interdisciplinary consultation are adequate. Some uncommon cases have been reported in which the tumor has grown more aggressively. These tumors may require therapeutic interventions (e.g., vitreoretinal surgery, brachytherapy, photodynamic therapy, or cryotherapy).

Journal Title: Der Ophthalmologe : Zeitschrift der Deutschen Ophthalmologischen Gesellschaft

PUBMED ID: 19476269

DOI: Mancante

Titolo: Current status and future potential of advanced technologies in radiation oncology. Part 2. State of the science by anatomic site.

Autori: Vikram B., Coleman CN., Deye JA.

Data di Pubblicazione: 2009-5-30

Abstract: In December 2006, the Radiation Research Program of the Division of Cancer Treatment and Diagnosis of the National Cancer Institute hosted a workshop intended to address current issues related to advanced radiation therapy technologies, with an eye toward (1) defining the specific toxicities that have limited the success of "conventional" radiation therapy, (2) examining the evidence from phase III studies for the improvements attributed to the advanced technologies in the treatment of several cancers commonly treated with radiation therapy, and (3) determining the opportunities and priorities for further technologic development and clinical trials. The new technologies offer substantial theoretical advantage in radiation dose distributions that, if realized in clinical practice, may help many cancer patients live longer and/or better. The precision of the advanced technologies may allow us to reduce the volume of normal tissue irradiated in the vicinity of the clinical target volume. Part 1 of this two-part article, which appeared in the March issue of ONCOLOGY, provided a general overview of the workshop discussion, focusing on the challenges posed by the new technologies and resources available or in development for meeting those challenges. This month, part 2 will outline the state of the science for each disease site.

Journal Title: Oncology (Williston Park, N.Y.)

PUBMED ID: 19465788

DOI: doi.org/10.2176/nmc.49.193

Titolo: Pharmacokinetic investigation of increased efficacy against malignant gliomas of carboplatin combined with hyperbaric oxygenation.

Autori: Suzuki Y., Tanaka K., Negishi D., Shimizu M., Yoshida Y., Hashimoto T., Yamazaki H.

Data di Pubblicazione: 2009-5-26

Abstract: The efficacy of intravenous administration of 400 mg carboplatin/m<sup>2</sup> (2) body surface area over 60 minutes combined with hyperbaric oxygenation (HBO) therapy (0.2 MPa for 60 min) was investigated in 6 Japanese patients (aged 36-67 years) with malignant or brainstem gliomas. Plasma ultra-filtrate samples were analyzed by high-performance liquid chromatography to evaluate the relationship between efficacy and pharmacokinetics. Brain tumor response was evaluated by magnetic resonance imaging as a function of maximum plasma concentration, area under the curve, or mean residence time (MRT) for carbop

latin. The MRT for carboplatin in the complete or partial response group (mean  $\pm$  standard deviation 4.3  $\pm$  1.7 hrs; 6 courses in 3 patients) was significantly longer ( $p < 0.05$ ) than that in the progressive disease group (2.4  $\pm$  0.1 hrs; 3 courses in 3 patients), but maximum plasma concentration and area under the curve showed no differences. These results suggest that HBO therapy prolongs the biological residence time of carboplatin. MRT for carboplatin may be useful for predicting continuation or modification of chemotherapy and/or clinical antitumor effects in patients with malignant gliomas.  
Journal Title: Neurologia medico-chirurgica

PUBMED ID: 19464817  
DOI: doi.org/10.1016/j.ijrobp.2009.01.079  
Titolo: Factors associated with neurological recovery of brainstem function following postoperative conformal radiation therapy for infratentorial ependymoma.  
Autori: Merchant TE., Chitti RM., Li C., Xiong X., Sanford RA., Khan RB.  
Data di Pubblicazione: 2009-5-26  
Abstract: Incomplete recovery of brainstem function after CRT for infratentorial ependymoma is related to surgical morbidity and the volume and the extent of tumor.  
Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 19415180  
DOI: doi.org/10.1007/s00701-009-0306-5  
Titolo: Combined multiple surgical intervention and chemotherapy for multicentric WHO grade II glioma : a long-term follow-up study.  
Autori: Vergani F., Sanson M., Duffau H.  
Data di Pubblicazione: 2009-5-6  
Abstract: The problems concerning the pathophysiology, diagnosis and treatment of this condition are discussed. On the basis of our results, we suggest that an active therapeutic strategy, by combining multiple surgical procedures and complementary treatment, should be systematically considered in multicentric WHO grade II gliomas, as in similar unifocal neoplasms.  
Journal Title: Acta neurochirurgica

PUBMED ID: 19414327  
DOI: Mancante  
Titolo: Efficacy of temozolomide treatment in patients with high-grade glioma.  
Autori: Oshiro S., Tsugu H., Komatsu F., Ohmura T., Ohta M., Sakamoto S., Fukushima T., Inoue T.  
Data di Pubblicazione: 2009-5-6  
Abstract: TMZ chemotherapy is effective for the treatment of high-grade glioma in some patients without serious toxicity. Assessing the true efficacy of TMZ will require a larger study with comparison of long-term outcomes between other agents or combined therapeutic modalities.  
Journal Title: Anticancer research

PUBMED ID: 21475844  
DOI: doi.org/10.3892/mmr\_00000115  
Titolo: Salvage therapy with temozolomide for recurrent or progressive high-grade gliomas refractory to ACNU [1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride].  
Autori: Terasaki M., Tokutomi T., Shigemori M.  
Data di Pubblicazione: 2011-4-9

**Abstract:** This study aimed to determine safety, response rate, toxicity and 6-month progression-free survival (PFS) by using temozolomide (TMZ) as salvage chemotherapy for 25 adults with recurrent or progressive high-grade gliomas (HGGs) who failed 1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU) therapy. Twenty-six patients with recurrent or progressive ACNU refractory HGG, including 12 with glioblastoma (GBM) and 13 with anaplastic astrocytoma (AA) were evaluated in a prospective study of temozolomide salvage chemotherapy. Following maximal surgical resection, the patients received 2-4 cycles of procarbazine (100 mg/m<sup>2</sup>, days 1-5), ACNU (80 mg/m<sup>2</sup>/d1, day 5) and, on days 5 and 12, cephazolin (70 mg) and vincristine (1.4 mg/m<sup>2</sup>). TMZ (150-200 mg/m<sup>2</sup>/d, days 1-5) was also administered every 28 days for ≤24 cycles. The six-month PFS was 50% (mean 10 months; 95% CI, 7-14 months) in 12 GBM patients and 39% (mean 17 months; 95% CI, 7-28 months) in 13 patients with AA. The best response to chemotherapy had no impact on the duration of disease control. Treatment-related toxicities included infections, while two (8%) patients developed neutropenia. In conclusion, TMZ can benefit patients with ACNU refractory HGG.

**Journal Title:** Molecular medicine reports

PUBMED ID: 19360418  
DOI: doi.org/10.1007/s00381-009-0882-y  
**Titolo:** Surgical considerations of spinal ependymomas in the pediatric population.  
**Autori:** Hsu W., Pradilla G., Constantini S., Jallo GI.  
**Data di Pubblicazione:** 2009-4-11  
**Abstract:** Patients requiring multilevel laminectomy may benefit from concomitant laminoplasty or instrumented fusion to avoid progressive spinal column deformity.  
**Journal Title:** Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 19351370  
DOI: doi.org/10.1111/j.1440-1827.2009.02360.x  
**Titolo:** Medulloblastoma with myogenic differentiation showing double immunopositivity for synaptophysin and myoglobin.  
**Autori:** Kido M., Ueno M., Onodera M., Matsumoto K., Imai T., Haba R., Tamiya T., Huang CL., Sakamoto H.  
**Data di Pubblicazione:** 2009-4-9  
**Abstract:** Reported herein is a case of medulloblastoma with myogenic differentiation in a 3-year-old girl who died 1 year after appearance of clinical signs. Magnetic resonance imaging indicated a mass lesion in the cerebellar vermis. She underwent total resection of the tumor, followed by chemotherapy and radiotherapy in the brain and spinal cord. The resected specimen mainly consisted of densely packed cells with round-to-oval highly chromatic nuclei surrounded by scanty cytoplasm and focally of long spindle-shaped cells with elongated nuclei and eosinophilic cytoplasm showing discernible cross-striations. Immunohistochemistry indicated partial expression of synaptophysin in the former area and focal expression of desmin in the latter area. The diagnosis was medulloblastoma with myogenic differentiation, also known as medulloblastoma. Autopsy indicated disseminated proliferation of immature neuroglial cells with highly chromatic nuclei and scanty cytoplasm showing partial expression of synaptophysin, neurofilaments, and GFAP, and focal proliferation of round-to-oval immature cells showing immunoreactivity of myoglobin. The tumor cells had large nuclei, frequent mitoses, apoptoses, nuclear molding, and cell wrapping, indicating moderate anaplasia. Their Ki-67 labeling index was 54%. In addition, some tumor cells had double immunopositivity for synaptophysin or neurofilament and myoglobin, suggesting that the neuroectodermal cells may undergo differentiation into rhabdomyoblasts.

Journal Title: Pathology international

PUBMED ID: 19335893

DOI: doi.org/10.1186/1471-2407-9-101

Titolo: Treatment of recurrent malignant gliomas with fotemustine monotherapy: impact of dose and correlation with MGMT promoter methylation.

Autori: Fabi A., Metro G., Russillo M., Vidiri A., Carapella CM., Maschio M., Cognetti F., Jandolo B., Mirri MA., Sperduti I., Telera S., Carosi M., Pace A.

Data di Pubblicazione: 2009-4-2

Abstract: Low-dose fotemustine at 65-75 mg/m<sup>2</sup> (induction phase) followed by 75-85 mg/m<sup>2</sup> (maintenance phase) has an activity comparable to that of the conventional schedule. By determination of the MGMT promoter methylation status patients might be identified who are more likely to benefit from fotemustine chemotherapy.

Journal Title: BMC cancer

PUBMED ID: 19307505

DOI: doi.org/10.1200/JCO.2008.19.0694

Titolo: Phase II trial of vorinostat in recurrent glioblastoma multiforme: a north central cancer treatment group study.

Autori: Galanis E., Jaeckle KA., Maurer MJ., Reid JM., Ames MM., Hardwick JS., Reilly JF., Loboda A., Nebozhyn M., Fantin VR., Richon VM., Scheithauer B., Giannini C., Flynn PJ., Moore DF., Zwiebel J., Buckner JC.

Data di Pubblicazione: 2009-3-25

Abstract: Vorinostat monotherapy is well tolerated in patients with recurrent GBM and has modest single-agent activity. Histone acetylation analysis and RNA expression profiling indicate that vorinostat in this dose and schedule affects target pathways in GBM. Additional testing of vorinostat in combination regimens is warranted.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 19289491

DOI: doi.org/10.1215/15228517-2009-007

Titolo: Phase I trial of temozolomide plus O(6)-benzylguanine 5-day regimen with recurrent malignant glioma.

Autori: Quinn JA., Jiang SX., Reardon DA., Desjardins A., Vredenburgh JJ., Rich JN., Gururangan S., Friedman AH., Bigner DD., Sampson JH., McLendon RE., Herndon JE., Walker A., Friedman HS.

Data di Pubblicazione: 2009-3-18

Abstract: This phase I clinical trial conducted with patients who had recurrent or progressive malignant glioma (MG) was designed to determine the maximum tolerated dose (MTD) and toxicity of three different 5-day dosing regimens of temozolomide (TMZ) in combination with O(6)-benzylguanine (O(6)-BG). Both TMZ and O(6)-BG were administered on days 1-5 of a 28-day treatment cycle. A bolus infusion of O(6)-BG was administered at 120 mg/m<sup>2</sup> over 1 h on days 1, 3, and 5, along with a continuous infusion of O(6)-BG at 30 mg/m<sup>2</sup>/day. TMZ was administered at the end of the first bolus infusion of O(6)-BG and then every 24 h for 5 days during the continuous infusion of O(6)-BG. Patients were accrued to one of three 5-day dosing regimens of TMZ. Twenty-nine patients were enrolled into this study. The dose-limiting toxicities (DLTs) were grade 4 neutropenia, leukopenia, and thrombocytopenia. The MTD for TMZ for the three different 5-day dosing schedules was determined as follows: schedule 1, 200 mg/m<sup>2</sup> on day 1 and 50 mg/m<sup>2</sup>/day on days 2-5; schedule 2, 50 mg/m<sup>2</sup>/day on days 1-5; and schedule 3, 50 mg/m<sup>2</sup>/day on days 1-5 while receiving pegfilgrastim. Thus, the 5-day TMZ dosing schedule that maximized



the total dose of TMZ when combined with O(6)-BG was schedule 1. This study provides the foundation for a phase II trial of O(6)-BG in combination with a 5-day dosing schedule of TMZ in TMZ-resistant MG.

Journal Title: Neuro-oncology

PUBMED ID: 19260101

DOI: doi.org/10.1002/pbc.21987

Titolo: Interferon-beta, MCNU, and conventional radiotherapy for pediatric patients with brainstem glioma.

Autori: Ohno M., Natsume A., Fujii M., Ito M., Wakabayashi T.

Data di Pubblicazione: 2009-3-5

Abstract: The IMR combination therapy is well tolerated and may be a promising treatment for brainstem glioma.

Journal Title: Pediatric blood & cancer

PUBMED ID: 19252415

DOI: doi.org/10.4161/cbt.8.8.7927

Titolo: Pro-survival AKT and ERK signaling from EGFR and mutant EGFRvIII enhances DNA double-strand break repair in human glioma cells.

Autori: Golding SE., Morgan RN., Adams BR., Hawkins AJ., Povirk LF., Valerie K.

Data di Pubblicazione: 2009-3-3

Abstract: The epidermal growth factor receptor (EGFR) is frequently dysregulated in malignant glioma that leads to increased resistance to cancer therapy. Upregulation of wild type or expression of mutant EGFR is associated with tumor radioresistance and poor clinical outcome. EGFR variant III (EGFRvIII) is the most common EGFR mutation in malignant glioma. Radioresistance is thought to be, at least in part, the result of a strong cytoprotective response fueled by signaling via AKT and ERK that is heightened by radiation in the clinical dose range. Several groups including ours have shown that this response may modulate DNA repair. Herein, we show that expression of EGFRvIII promoted gamma-H2AX foci resolution, a surrogate for double-strand break (DSB) repair, and thus enhanced DNA repair. Conversely, small molecule inhibitors targeting EGFR, MEK, and the expression of dominant-negative EGFR (EGFR-CD53) significantly reduced the resolution of gamma-H2AX foci. When homologous recombination repair (HRR) and non-homologous end joining (NHEJ) were specifically examined, we found that EGFRvIII stimulated and CD533 compromised HRR and NHEJ, respectively. Furthermore, NHEJ was blocked by inhibitors of AKT and ERK signaling pathways. Moreover, expression of EGFRvIII and CD533 increased and reduced, respectively, the formation of phospho-DNA-PKcs and -ATM repair foci, and RAD51 foci and expression levels, indicating that DSB repair is regulated at multiple levels. Altogether, signaling from EGFR and EGFRvIII promotes both HRR and NHEJ that is likely a contributing factor towards the radioresistance of malignant gliomas.

Journal Title: Cancer biology & therapy

PUBMED ID: 19250783

DOI: doi.org/10.1016/j.ejrad.2009.01.013

Titolo: Glioblastoma treated with postoperative radio-chemotherapy: prognostic value of apparent diffusion coefficient at MR imaging.

Autori: Yamasaki F., Sugiyama K., Ohtaki M., Takeshima Y., Abe N., Akiyama Y., Takaba J., Amatya VJ., Saito T., Kajiwara Y., Hanaya R., Kurisu K.

Data di Pubblicazione: 2009-3-3

Abstract: The ADC(MIN) value obtained from pretreatment MR images is a useful clinical prognostic biomarker in patients with glioblastoma.

Journal Title: European journal of radiology

PUBMED ID: 19240962

DOI: doi.org/10.1007/s00415-009-5006-9

Titolo: Rechallenge with temozolomide in patients with recurrent gliomas.

Autori: Wick A., Pascher C., Wick W., Jauch T., Weller M., Bogdahn U., Hau P.

Data di Pubblicazione: 2009-2-26

Abstract: Temozolomide (TMZ) is the standard of care for patients with newly diagnosed glioblastoma (GBM) as well as those with recurrent anaplastic glioma (AG) and GBM. It has become common practice to re-expose patients to TMZ who had been previously treated with TMZ, or to switch patients to alternative dosing regimens of TMZ when there are signs of relapse or progress on standard TMZ therapeutic regimens. To date, however, there is a scarcity of data on the efficacy of this therapeutic strategy, currently referred to as TMZ rechallenge. We have conducted a retrospective review of patients with recurrent glioma rechallenged with TMZ. Patients experiencing progressive disease (PD) during TMZ therapy who were rechallenged with alternative TMZ regimens and patients rechallenged after stable disease in a TMZ-free interval were evaluated separately. A total of 90 rechallenges were identified in 80 patients. The progression-free survival at 6 months (PFS-6) was 48% in patients with AG (12/25) and 27.7% in those with GBM (14/47). The PFS-6 was 16.7% in AG and 26.3% in GBM for patients switched during TMZ and 57.9 and 28.6% in patients rechallenged after a TMZ-free interval of at least 8 weeks. Relevant hematological toxicity (NCI-CTC grade 3-5) was observed in 22 of 90 rechallenges, and relevant non-hematological in ten of 90 rechallenges. Temozolomide was well tolerated and generated promising PFS-6 in patients who had previously failed TMZ, regardless if they progressed during TMZ treatment, or if they were rechallenged after a TMZ-free interval. These results suggest that the TMZ rechallenge strategy warrants further investigation in a prospective randomized trial.

Journal Title: Journal of neurology

PUBMED ID: 19221865

DOI: doi.org/10.1007/s11060-009-9809-4

Titolo: Effect of adding temozolomide to radiation therapy on the incidence of pseudo-progression.

Autori: Gerstner ER., McNamara MB., Norden AD., Lafrankie D., Wen PY.

Data di Pubblicazione: 2009-2-18

Abstract: Recently, there has been greater awareness that combination radiation and temozolomide used to treat glioblastomas may cause increased contrast enhancement on the first post radiation MRI scan. However, this increased enhancement may stabilize or decrease over time and represent pseudo-progression (psPD) rather than true progressive disease. It has never been shown that this phenomenon is greater with combination therapy than radiation alone. To address this question, we reviewed MRI scans in glioblastoma patients treated with radiation alone versus patients treated with radiation and concomitant temozolomide and compared the frequency of psPD in the two groups. Eighteen of 47 patients (38%) treated with radiation alone demonstrated enlargement on their first post-radiation MRI scan and 11 of these 18 (61%) proved to have psPD as defined by no further enlargement on stable therapy for 3 months following radiation. Twenty-four of 45 patients (53%) treated with radiation and temozolomide had enlargement on their first post-radiation MRI scan and 13 of these 24 (54%) had psPD. Median overall survival (OS) in patients with psPD treated with radiation alone was 15.6 versus 12.8 months in those without psPD. Median OS in patients treated with radiation and concomitant temozolomide who had psPD was 24.4 versus 15.9 months in those who did not have psPD. We were unable to detect a difference in OS between the four groups. Presence of psPD, independent of treatment, was associated with prolonged

progression-free survival (P = 0.05) but not OS. psPD may be more common in combination therapy but most likely by a small margin.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 19204207  
DOI: doi.org/10.1200/JCO.2008.17.5984  
Titolo: Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034.  
Autori: van den Bent MJ., Brandes AA., Rampling R., Kouwenhoven MC., Kros JM., Carpentier AF., Clement PM., Frenay M., Campone M., Baurain JF., Armand J P., Taphoorn MJ., Tosoni A., Kletzl H., Klughammer B., Lacombe D., Gorlia T.  
Data di Pubblicazione: 2009-2-11  
Abstract: Erlotinib has insufficient single-agent activity in unselected GBM. No clear biomarker associated with improved outcome to erlotinib was identified.  
Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 19197992  
DOI: doi.org/10.1002/cncr.24179  
Titolo: Bevacizumab for recurrent alkylator-refractory anaplastic oligodendroglioma.  
Autori: Chamberlain MC., Johnston S.  
Data di Pubblicazione: 2009-2-7  
Abstract: Bevacizumab demonstrated efficacy and acceptable toxicity in this cohort of adults with recurrent lp19q codeleted alkylator-refractory AO.  
Journal Title: Cancer

PUBMED ID: 19192961  
DOI: doi.org/10.1586/14737140.9.2.235  
Titolo: Interactions between PTEN and receptor tyrosine kinase pathways and their implications for glioma therapy.  
Autori: Abounader R.  
Data di Pubblicazione: 2009-2-6  
Abstract: Gliomas are the most common and deadly form of malignant primary brain tumors. Loss of the tumor-suppressor PTEN and activation of the receptor tyrosine kinases (RTKs) EGF receptor, c-Met, PDGF receptor and VEGF receptor are among the most common molecular dysfunctions associated with glioma malignancy. PTEN interacts with RTK-dependent signaling at multiple levels. These include the ability of PTEN to counteract PI3K activation by RTKs, as well as possible effects of PTEN on RTK activation of the MAPK pathway and RTK-dependent gene-expression regulation. Consequently, PTEN expression affects RTK-induced malignancy. Importantly, the PTEN status was recently found to be critical for the outcome of RTK-targeted clinical therapies that have been developed recently. Combining RTK-targeted therapies with therapies aimed at counteracting the effects of PTEN loss, such as mTOR inhibition, might also have therapeutic advantage. This article reviews the known molecular and functional interactions between PTEN and RTK pathways and their implications for glioma therapy.  
Journal Title: Expert review of anticancer therapy

PUBMED ID: 19190249  
DOI: doi.org/10.1182/blood-2008-07-171389  
Titolo: Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors.

Autori: Golden EB., Lam PY., Kardosh A., Gaffney KJ., Cadenas E., Louie SG., Petasis NA., Chen TC., Schönthal AH.

Data di Pubblicazione: 2009-2-5

Abstract: The anticancer potency of green tea and its individual components is being intensely investigated, and some cancer patients already self-medicate with this "miracle herb" in hopes of augmenting the anticancer outcome of their chemotherapy. Bortezomib (BZM) is a proteasome inhibitor in clinical use for multiple myeloma. Here, we investigated whether the combination of these compounds would yield increased antitumor efficacy in multiple myeloma and glioblastoma cell lines in vitro and in vivo. Unexpectedly, we discovered that various green tea constituents, in particular (-)-epigallocatechin gallate (EGCG) and other polyphenols with 1,2-benzenediol moieties, effectively prevented tumor cell death induced by BZM in vitro and in vivo. This pronounced antagonistic function of EGCG was evident only with boronic acid-based proteasome inhibitors (BZM, MG-262, PS-IX), but not with several non-boronic acid proteasome inhibitors (MG-132, PS-I, nelfinavir). EGCG directly reacted with BZM and blocked its proteasome inhibitory function; as a consequence, BZM could not trigger endoplasmic reticulum stress or caspase-7 activation, and did not induce tumor cell death. Taken together, our results indicate that green tea polyphenols may have the potential to negate the therapeutic efficacy of BZM and suggest that consumption of green tea products may be contraindicated during cancer therapy with BZM.

Journal Title: Blood

PUBMED ID: 19169684

DOI: doi.org/10.1007/s00280-009-0926-8

Titolo: Fotemustine as second-line treatment for recurrent or progressive glioblastoma after concomitant and/or adjuvant temozolomide: a phase II trial of Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO).

Autori: Brandes AA., Tosoni A., Franceschi E., Blatt V., Santoro A., Faedi M., Amistà P., Gardiman M., Labianca R., Bianchini C., Ermani M., Reni M.

Data di Pubblicazione: 2009-1-27

Abstract: The findings of the present trial, that evaluate fotemustine in a homogeneous population, may represent a new benchmark for nitrosourea activity. Moreover, this is the first study to evaluate correlation between MGMT promoter status and outcome of fotemustine for relapsing GBM previously treated with radiotherapy and temozolomide.

Journal Title: Cancer chemotherapy and pharmacology

PUBMED ID: 19165892

DOI: doi.org/10.1002/pbc.21935

Titolo: Objective response of multiply recurrent low-grade gliomas to bevacizumab and irinotecan.

Autori: Packer RJ., Jakacki R., Horn M., Rood B., Vezina G., MacDonald T., Fisher MJ., Cohen B.

Data di Pubblicazione: 2009-1-24

Abstract: Multiply recurrent low-grade gliomas in children are responsive to the combination of bevacizumab and irinotecan. The drug combination has been relatively well tolerated, including in patients with neurofibromatosis type 1, and warrants further study.

Journal Title: Pediatric blood & cancer

PUBMED ID: 19164435

DOI: doi.org/10.1215/15228517-2008-114

Titolo: Plasma IGFBP-2 levels predict clinical outcomes of patients with high-grade gliomas.

Autori: Lin Y., Jiang T., Zhou K., Xu L., Chen B., Li G., Qiu X., Jiang T., Zhang W., Song SW.

Data di Pubblicazione: 2009-1-24

Abstract: Insulin-like growth factor binding protein 2 (IGFBP-2) is a malignancy-associated protein measurable in tumors and blood. Increased IGFBP-2 is associated with shortened survival of advanced glioma patients. Thus, we examined plasma IGFBP-2 levels in glioma patients and healthy controls to evaluate its value as a plasma biomarker for glioma. Plasma IGFBP-2 levels in 196 patients with newly diagnosed glioma and 55 healthy controls were analyzed using an IGFBP-2 ELISA kit. Blood was collected before surgery, after two-cycle adjuvant chemotherapy, and at recurrence. Plasma IGFBP-2 levels were correlated with disease-free survival (DFS) using Cox regression analyses. We found that preoperative plasma IGFBP-2 levels were significantly higher in high-grade glioma patients (n = 43 for grade III glioma; n = 72 for glioblastoma multiforme [GBM]) than in healthy controls (n = 55; p < 0.001) and low-grade (grade II) glioma patients (n = 81; p < 0.001). No significant differences in preoperative plasma IGFBP-2 levels were observed between grade III glioma and GBM patients or between grade II glioma patients and healthy controls. After recurrence, plasma IGFBP-2 levels were significantly increased in GBM patients (n = 26; p < 0.001). Preoperative plasma IGFBP-2 levels were significantly correlated with DFS in GBM patients (hazard ratio, 1.404; 95% confidence interval, 1.078-1.828; p = 0.012). We conclude that preoperative plasma IGFBP-2 levels are significantly higher in high-grade glioma patients than in low-grade glioma patients and healthy subjects, and are significantly correlated with recurrence and DFS in patients with GBM. Longitudinal studies with a larger study population are needed to confirm these findings.

Journal Title: Neuro-oncology

PUBMED ID: 19139825

DOI: doi.org/10.1007/s11060-008-9774-3

Titolo: Topotecan in combination with radiotherapy in unresectable glioblastoma: a phase 2 study.

Autori: Lesimple T., Riffaud L., Frappaz D., Ben Hassel M., Gédouin D., Bay JO., Linassier C., Hamlat A., Piot G., Fabbro M., Saïkali S., Carsin B., Guégan Y.

Data di Pubblicazione: 2009-1-14

Abstract: Improving glioblastoma multiforme (GBM) treatment with radio-chemotherapy remains a challenge. Topotecan is an attractive option as it exhibits growth inhibition of human glioma as well as brain penetration. The present study assessed the combination of radiotherapy (60 Gy/30 fractions/40 days) and topotecan (0.9 mg/m<sup>2</sup>/day on days 1-5 on weeks 1, 3 and 5) in 50 adults with histologically proven and untreated GBM. The incidence of non-hematological toxicities was low and grade 3-4 hematological toxicities were reported in 20 patients (mainly lymphopenia and neutropenia). Partial response and stabilization rates were 2% and 32%, respectively, with an overall time to progression of 12 weeks. One-year overall survival (OS) rate was 42%, with a median OS of 40 weeks. Topotecan in combination with radiotherapy was well tolerated. However, while response and stabilization concerned one-third of the patients, the study did not show increased benefits in terms of survival in patients with unresectable GBM.

Journal Title: Journal of neuro-oncology

PUBMED ID: 19118062

DOI: doi.org/10.1158/1078-0432.CCR-08-0888

Titolo: Phase II study of protracted daily temozolomide for low-grade gliomas in adults.

Autori: Kesari S., Schiff D., Drappatz J., LaFrankie D., Doherty L., Macklin EA., Muzikansky A., Santagata S., Ligon KL., Norden AD., Ciampa A., Bradshaw J., Levy B., Radakovic G., Ramakrishna N., Black PM., Wen PY.

Data di Pubblicazione: 2009-1-2

Abstract: A protracted course of daily temozolomide is a well-tolerated regimen and seems to produce effective tumor control. This compares favorably with historical data on the standard 5-day temozolomide regimen.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 19116635

DOI: doi.org/10.1038/mt.2008.275

Titolo: Phase I trial of oncolytic herpes virus G207 shows safety of multiple injections and documents viral replication.

Autori: Aghi MK., Chiocca EA.

Data di Pubblicazione: 2009-1-1

Abstract:

Journal Title: Molecular therapy : the journal of the American Society of Gene Therapy

PUBMED ID: 19075266

DOI: doi.org/10.1200/JCO.2008.18.4176

Titolo: Hyperfractionated accelerated radiotherapy in the Milan strategy for metastatic medulloblastoma.

Autori: Gandola L., Massimino M., Cefalo G., Solero C., Spreafico F., Pecori E., Riva D., Collini P., Pignoli E., Giangaspero F., Luksch R., Berretta S., Poggi G., Biassoni V., Ferrari A., Pollo B., Favre C., Sardi I., Terenziani M., Fossati-Bellani F.

Data di Pubblicazione: 2008-12-17

Abstract: HART after intensive postoperative chemotherapy, followed by myeloablative chemotherapy in selected cases, proved feasible in children with metastatic medulloblastoma. The results of our treatment compare favorably with other series treated using conventional therapies.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 19062723

DOI: Mancante

Titolo: [Multicenter phase II clinical trial of uroacitides injection in the treatment for advanced malignant tumors].

Autori: Li Q., Feng FY., Chen Q., Jiao SC., Li F., Wang HQ., Huang WX., Ling CQ., Li MZ., Ren J., Zhang Y., Qin FZ., Zhou MZ., Zhu RZ.

Data di Pubblicazione: 2008-12-10

Abstract: Uroacitides injection is effective in the control for various kinds of advanced cancers with mild, reversible and tolerable adverse effects, and can also improve the patient's quality of life. It is worth being studied further.

Journal Title: Zhonghua zhong liu za zhi [Chinese journal of oncology]

PUBMED ID: 19061223

DOI: doi.org/10.1002/pbc.21881

Titolo: Tumor stabilization under treatment with imatinib in progressive hypothalamic-chiasmatic glioma.

Autori: Peyrl A., Azizi A., Czech T., Gruber-Olipitz M., Jones N., Haberler C., Prayer D., Autzinger E., Slavc I.

Data di Pubblicazione: 2008-12-9

Abstract: We conclude that imatinib has possible activity in progressive HCG and may present an additional therapeutic option for patients who are too young or whose tumor is too extensive to receive radiotherapy. However, the optimal use of imatinib in this disease, its mechanism of action, and possible long-term effects remain unclear and will require additional study.

Journal Title: Pediatric blood & cancer

PUBMED ID: 19057330

DOI: doi.org/10.1227/01.NEU.0000334052.60634.84

Titolo: Intraparenchymal and intratumoral interstitial infusion of anti-glioma monoclonal antibody 8H9.

Autori: Luther N., Cheung NK., Dunkel IJ., Fraser JF., Edgar MA., Gutin PH., Souweidane MM.

Data di Pubblicazione: 2008-12-6

Abstract: Finally, intratumoral interstitial infusion of a reactive MAb has been performed similarly to delivery to a normal brain. This finding is encouraging from a therapeutic standpoint, given the clinical need to affect large domains of these infiltrative tumors.

Journal Title: Neurosurgery

PUBMED ID: 19031176

DOI: doi.org/10.1080/02841860802537924

Titolo: Bevacizumab plus irinotecan in the treatment patients with progressive recurrent malignant brain tumours.

Autori: Poulsen HS., Grunnet K., Sorensen M., Olsen P., Hasselbalch B., Nelausen K., Kosteljanetz M., Lassen U.

Data di Pubblicazione: 2008-11-26

Abstract: We conclude that the combination of bevacizumab and irinotecan shows acceptable safety and is a clinically relevant choice of therapy in heavily pre-treated patients with recurrent high-grade brain tumours.

Journal Title: Acta oncologica (Stockholm, Sweden)

PUBMED ID: 19025795

DOI: doi.org/10.1002/gcc.20635

Titolo: Stepwise accumulation of distinct genomic aberrations in a patient with progressively metastasizing ependymoma.

Autori: Milde T., Pfister S., Korshunov A., Deubzer HE., Oehme I., Ernst A., Starzinski-Powitz A., Seitz A., Lichter P., von Deimling A., Witt O.

Data di Pubblicazione: 2008-11-26

Abstract: Nonresectable ependymomas are associated with poor prognosis despite intensive radiochemotherapy and radiation. The molecular pathogenesis of ependymoma initiation and progression is largely unknown. We here present a case of therapy-refractory, progressive ependymoma with cerebrospinal as well as extraneural metastases, which allowed us for the first time to follow the stepwise accumulation of chromosome aberrations during disease progression. Genome-wide DNA copy-number analysis showed sequential deletions on chromosomes 1, 9, and 14 as well as a homozygous deletion of the CDKN2A locus, underscoring its role in tumor progression. Gradual loss at 1p36 was associated with loss of protein expression of the putative tumor suppressor gene AJAP1/SHREW1. In summary, this is the first report on acquired genomic aberrations in ependymoma over time pointing to novel candidate tumor suppressor genes. This analysis provides molecular insights into the chronology of genetic events in this case from initial localized tumor to widespread metastasized disease.

Journal Title: Genes, chromosomes & cancer

PUBMED ID: 19018476

DOI: doi.org/10.1007/s11060-008-9739-6

Titolo: A multi-institutional phase II study on second-line Fotemustine chemotherapy in recurrent glioblastoma.

Autori: Fabrini MG., Silvano G., Lolli I., Perrone F., Marsella A., Scotti V., Cionini L.

Data di Pubblicazione: 2008-11-20

Abstract: The present study aims to assess the feasibility and the effectiveness of a second-line Fotemustine chemotherapy in patients with recurrent Glioblastoma after standard primary treatment. Between 2005 and 2007, 50 patients with relapsed malignant glioma (median age=56.8 years; median KPS=90) underwent a second-line chemotherapy with Fotemustine. Selected patients were previously treated with a standard 60 Gy Radiotherapy course and Temozolomide Chemotherapy. Patients were stratified into classes according to the prognostic Recursive Partition Analysis. Endpoints of the study were Progression Free Survival at 6 months, duration of Objective Response and Stabilization, Overall Survival and toxicity. At analysis, 36 patients were dead and 14 were alive. Median follow-up from primary diagnosis was 26.6 months. The Efficacy control of the disease was 62%. PFS was 6.1 months; PFS-6 was 52% and median overall survival from primary diagnosis was 24.5 months, with few manageable haematological toxicities. Fotemustine was safe and effective as second-line chemotherapy in recurrent glioblastoma.

Journal Title: Journal of neuro-oncology

PUBMED ID: 18990510

DOI: doi.org/10.1016/j.ijrobp.2008.05.030

Titolo: The role of hypofractionation radiotherapy for diffuse intrinsic brainstem glioma in children: a pilot study.

Autori: Janssens GO., Gidding CE., Van Lindert EJ., Oldenburger FR., Erasmus CE., Schouten-Meeteren AY., Kaanders JH.

Data di Pubblicazione: 2008-11-8

Abstract: This radical hypofractionation radiotherapy regimen for children with diffuse intrinsic brainstem glioma is feasible and associated with no Grade 3 or 4 toxicities. With a minimal overall treatment time, it offers quick symptom relief and outcome results within the range of published data.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 18987781

DOI: doi.org/10.1007/s11060-008-9728-9

Titolo: ACNU-based chemotherapy for recurrent glioma in the temozolomide era.

Autori: Happold C., Roth P., Wick W., Steinbach JP., Linnebank M., Weller M., Eisele G.

Data di Pubblicazione: 2008-11-7

Abstract: No standard of care for patients with recurrent glioblastoma has been defined since temozolomide has become the treatment of choice for patients with newly diagnosed glioblastoma. This has renewed interest in the use of nitrosourea-based regimens for patients with progressive or recurrent disease. The most commonly used regimens are carmustine (BCNU) monotherapy or lomustine (CCNU) combined with procarbazine and vincristine (PCV). Here we report our institutional experience with nimustine (ACNU) alone (n=14) or in combination with other agents (n=18) in 32 patients with glioblastoma treated previously with temozolomide. There were no complete and two partial responses. The progression-free survival (PFS) rate at 6 months was 20% and the survival rate at 12 months 26%. Grade III or IV hematological toxicity was observed in 50% of all patients and led to interruption of treatment in 13% of patients. Non-hematological toxicity was moderate to severe and led to interruption of treatment in 9% of patients. Thus, in this cohort of patients pret



reated with temozolomide, ACNU failed to induce a substantial stabilization of disease in recurrent glioblastoma, but caused a notable hematotoxicity. This study does not commend ACNU as a therapy of first choice for patients with recurrent glioblastomas pretreated with temozolomide.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 21479498

DOI: doi.org/10.3892/mmr\_00000042

Titolo: Rechallenge with temozolomide with different scheduling is effective in recurrent malignant gliomas.

Autori: Strik HM., Buhk JH., Wrede A., Hoffmann AL., Bock HC., Christmann M., Kaina B.

Data di Pubblicazione: 2011-4-12

Abstract: Treatment of recurrent malignant glioma, which has a poor patient prognosis, has not been standardised. Moreover, it is unclear whether repeated treatment with temozolomide is effective in patients who received previous temozolomide treatment before developing a recurrence. Here, we present the results of a high-dose individually adapted 21-day regimen demonstrating that rechallenge is effective even in patients expressing O6-methylguanine-DNA methyltransferase (MGMT) in the tumor. Twenty-one patients with recurrent malignant gliomas pre-treated with temozolomide, 18 WHO IV glioblastoma (GBM) and 3 WHO III patients, received 100 mg/m<sup>2</sup> temozolomide on days 1-21/28. The GBM patients had a median Karnofsky performance status of 60% and a median age of 54.8 years. Blood counts decreased continuously, enabling a gradual dose adaptation. When blood counts dropped below normal values, temozolomide was applied on days 1-5/7. Dosage was reduced to 50-75 mg/m<sup>2</sup> in 11 patients and gradually increased up to 130 mg/m<sup>2</sup> in 3 patients. WHO grade 3/4 toxicity was hematological in 3 patients and non-hematological in 3 patients. In GBM patients (n=18), response after >3 months was complete in 3 patients, partial in 1 (22%), stable disease in 7 (39%) and progressive disease in 7 (39%). Progression-free survival at 6 months (PFS-6M) was 39%. Median survival was 9.1 months from relapse and 17.9 months overall. Of the patients with unmethylated MGMT promoter, 2/7 were progression-free for >6 (15 and 19) months. The data indicate that rechallenge with near-continuous, higher-dose temozolomide (100 mg/m<sup>2</sup> on days 1-21/28 or days 1-5/7 with individual dose adaptation) is also feasible in patients with critical blood counts. Objective responses can be achieved even after relapse during a conventional 5/28-day regimen. The resistance of tumors characterized by unmethylated MGMT promoter may be overcome by near continuous temozolomide administration, which is probably most effective with a 5/7-day schedule. In spite of the relatively poor clinical prognosis, the data indicate that rechallenge with temozolomide with a dose-dense and long-lasting administration protocol is tolerable and comparable with other reported treatment protocols involving temozolomide.

Journal Title: Molecular medicine reports

PUBMED ID: 18957964

DOI: doi.org/10.1038/mt.2008.228

Titolo: Phase Ib trial of mutant herpes simplex virus G207 inoculated pre- and post-tumor resection for recurrent GBM.

Autori: Markert JM., Liechty PG., Wang W., Gaston S., Braz E., Karrasch M., Nabors LB., Markiewicz M., Lakeman AD., Palmer CA., Parker JN., Whitley RJ., Gillespie GY.

Data di Pubblicazione: 2008-10-30

Abstract: We have previously demonstrated safety of G207, a doubly mutated (deletion of both gamma(1)34.5 loci, insertional inactivation of U(L)39) herpes simplex virus (HSV) for patients stereotactically inoculated in enhancing portions of recurrent malignant gliomas. We have now determined safety of two inoculations of G207, before and after tumor resection. Inclusion criteria

were histologically proven recurrent malignant glioma, Karnofsky score  $\geq 70$ , and ability to resect the tumor without ventricular system breach. Patients received two doses of G207 totaling  $1.15 \times 10^9$  plaque-forming units with 13% of this total injected via a catheter placed stereotactically in the tumor. Two or five days later, tumor was resected en bloc with catheter in place. The balance of G207 dose was injected into brain surrounding the resection cavity. Six patients with recurrent glioblastoma multiforme were enrolled. Two days after the second G207 inoculation, one patient experienced transient fever, delirium, and hemiparesis, which entirely resolved on high-dose dexamethasone. No patient developed HSV encephalitis or required treatment with acyclovir. Radiographic and neuropathologic evidence suggestive of antitumor activity is reported. Evidence of viral replication was demonstrated. G207 appears safe for multiple dose delivery, including direct inoculation into the brain surrounding tumor resection cavity.

Journal Title: Molecular therapy : the journal of the American Society of Gene Therapy

PUBMED ID: 18953491

DOI: doi.org/10.1007/s11060-008-9722-2

Titolo: Salvage chemotherapy with bevacizumab for recurrent alkylator-refractory anaplastic astrocytoma.

Autori: Chamberlain MC., Johnston S.

Data di Pubblicazione: 2008-10-28

Abstract: A retrospective study of bevacizumab only in adults with recurrent temozolomide (TMZ)-refractory anaplastic astrocytoma (AA) with a primary objective of determining progression free survival (PFS). There is no standard therapy for alkylator-resistant AA and hence a need exists for new therapies. Twenty-five patients (15 men; 10 women) ages 26-63 (median 50), with radiographically recurrent AA were treated. All patients had previously been treated with surgery, involved-field radiotherapy, and alkylator-based chemotherapy. Fourteen patients underwent repeat surgery. Patients were treated at second recurrence with bevacizumab (10 mg/kg), once every 2 weeks (defined as a single cycle). Neurological evaluation was performed every 2 weeks and neuroradiographic assessment following the initial two cycles of bevacizumab and subsequently after every four cycles of bevacizumab. All patients were evaluable for toxicity and response. A total of 360 cycles of bevacizumab (median 14 cycles; range 2-40) was administered. Bevacizumab-related toxicity included fatigue (14 patients; 2 grade 3), leukopenia (7; 1 grade 3), deep vein thrombosis (5; 2 grade 3), hypertension (5; 1 grade 3), anemia (4; 0 grade 3) and wound dehiscence (1; 1 grade 3). Sixteen patients (64%) demonstrated a partial radiographic response, 2 (8.0%) stable disease and 7 (28%) progressive disease following two cycles of bevacizumab. Time to tumor progression ranged from 1 to 20 months (median: 7). Survival ranged from 2 to 23 months (median: 9.0). 6-month and 12-month PFS were 60 and 20%, respectively. Bevacizumab demonstrated efficacy and acceptable toxicity in this cohort of adults with recurrent alkylator refractory AA.

Journal Title: Journal of neuro-oncology

PUBMED ID: 18928344

DOI: doi.org/10.1586/14737175.8.10.1507

Titolo: MRI for identification of progression in brain tumors: from morphology to function.

Autori: Weber MA., Giesel FL., Stieltjes B.

Data di Pubblicazione: 2008-10-22

Abstract: For monitoring of brain tumors, it is crucial to identify progression or treatment failure early during follow-up to change treatment schemes and, thereby, optimize patient outcome. In the past years, several areas within the field of magnetic resonance (MR) have seen considerable advances: mo

modern contrast media, advanced morphologic approaches and several functional techniques, for example, in the visualization of tumor perfusion or tumor cell metabolism. This review presents these recent advances by introducing the different techniques and outlining their benefit for identification of progression in brain tumors, with a focus on gliomas, metastases and meningiomas. After radiotherapy, MR spectroscopy helps to more accurately discriminate between radiation necrosis and glioma progression. In low-grade gliomas, perfusion MR techniques enable a more sensitive detection of anaplastic transformation than conventional MRI. Modern contrast media, as well as diffusion tensor imaging, allow for an improved tumor delineation and assessment of tumor extension. We will also highlight the biological background of these techniques, their applicability and current limitations. In conclusion, modern MRI techniques have been developed that are on the doorstep to be integrated in clinical routine.

Journal Title: Expert review of neurotherapeutics

PUBMED ID: 18834263

DOI: doi.org/10.3171/2008.4.17492

Titolo: Antiangiogenic therapy using bevacizumab in recurrent high-grade glioma: impact on local control and patient survival.

Autori: Narayana A., Kelly P., Golfinos J., Parker E., Johnson G., Knopp E., Zagzag D., Fischer I., Raza S., Medabalmi P., Eagan P., Gruber ML.

Data di Pubblicazione: 2008-10-7

Abstract: Antiangiogenic therapy using bevacizumab appears to improve survival in patients with recurrent high-grade glioma. A possible change in the invasiveness of the tumor following therapy is worrisome and must be closely monitored.

Journal Title: Journal of neurosurgery

PUBMED ID: 18828024

DOI: doi.org/10.1007/s00381-008-0716-3

Titolo: Malignant glioblastomatous transformation of a low-grade glioma in a child.

Autori: Unal E., Koksall Y., Cimen O., Paksoy Y., Tavli L.

Data di Pubblicazione: 2008-10-2

Abstract: The first line treatment modality in the management of low-grade glioma--especially in suitable patients--is clearly surgery. The gross total resection guarantees the distinguishing of the histological types of the low-grade gliomas and reflects the biologic behavior of these tumors. Observation without surgery must be reserved for selected inoperable cases.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 18797459

DOI: doi.org/10.1038/sj.bjc.6604652

Titolo: Telomere maintenance and dysfunction predict recurrence in paediatric ependymoma.

Autori: Tabori U., Wong V., Ma J., Shago M., Alon N., Rutka J., Bouffet E., Bartels U., Malkin D., Hawkins C.

Data di Pubblicazione: 2008-9-18

Abstract: We have recently described the enzymatic subunit of telomerase (hTERT) as an important prognostic marker for paediatric ependymoma. Because of the lack of good, representative pre-clinical models for ependymoma, we took advantage of our large cohort of ependymoma patients, some with multiple recurrences, to investigate telomere biology in these tumours. Our cohort consisted of 133 ependymomas from 83 paediatric patients and included 31 patients with recurrences. Clinical outcome was measured as overall survival, progres

sion-free survival and response to therapy. In all 133 tumours, hTERT expression correlated with proliferative markers, including MIB-1 index ( $P<0.0001$ ) and mitotic index ( $P=0.005$ ), as well as overall tumour grade ( $P=0.001$ ), but not with other markers of anaplasia. There was no correlation between telomere length and hTERT expression or survival. Surprisingly, prior radiation or chemotherapy neither induced sustained DNA damage nor affected telomere maintenance in recurrent tumours. There was an inverse correlation between hTERT expression and telomere dysfunction as measured by gamma H2AX expression ( $P=0.016$ ). Combining gamma H2AX and hTERT expressions could segregate tumours into three different survival groups (log rank,  $P<0.0001$ ) such that those patients whose tumours expressed hTERT and showed no evidence of DNA damage had the worst outcome. This study emphasises the importance of telomere biology as a prognostic tool and telomerase inhibition as a therapeutic target for paediatric ependymoma. Furthermore, we have demonstrated that analysing tumours as they progress in vivo is a viable approach to studying tumour biology in humans.

Journal Title: British journal of cancer

PUBMED ID: 18797358

DOI: doi.org/10.1227/01.NEU.0000315282.61035.48

Titolo: Persistent outpatient hyperglycemia is independently associated with decreased survival after primary resection of malignant brain astrocytomas.

Autori: McGirt MJ., Chaichana KL., Gathinji M., Attenello F., Than K., Jimenez Ruiz A., Olivi A., Quiñones-Hinojosa A.

Data di Pubblicazione: 2008-9-18

Abstract: In our experience, persistent outpatient hyperglycemia was associated with decreased survival in patients undergoing surgical resection for malignant astrocytomas and was independent of the degree of disability, tumour grade, diabetes, prolonged dexamethasone use, or subsequent treatment modalities. Increased glucose control is warranted in this patient population and may contribute to improved outcomes in the treatment of malignant brain astrocytomas.

Journal Title: Neurosurgery

PUBMED ID: 18769928

DOI: doi.org/10.1007/s00381-008-0707-4

Titolo: Responsiveness of progressive optic pathway tumors to cisplatin-based chemotherapy in children.

Autori: Hsu TR., Wong TT., Chang FC., Ho DM., Tang RB., Thien PF., Chang KP.

Data di Pubblicazione: 2008-9-5

Abstract: Cisplatin-based chemotherapy is an effective regimen for control of progressive optic pathway tumors.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 18751431

DOI: Mancante

Titolo: Influence of valproic acid on outcome of high-grade gliomas in children.

Autori: Masoudi A., Elope M., Amini E., Nagel ME., Ater JL., Gopalakrishnan V., Wolff JE.

Data di Pubblicazione: 2008-8-30

Abstract: Treatment with VPA plus radiochemotherapy is well tolerated with an encouraging response rate.

Journal Title: Anticancer research

PUBMED ID: 18726148

DOI: doi.org/10.1007/s00005-008-0027-0

Titolo: Ras pathway activation in gliomas: a strategic target for intranasal administration of perillyl alcohol.

Autori: da Fonseca CO., Linden R., Futuro D., Gattass CR., Quirico-Santos T.

Data di Pubblicazione: 2008-8-30

Abstract: The preliminary results indicate that intranasal administration of the signal transduction inhibitor POH is a safe, noninvasive, and low-cost method. There were no toxicity events and the regression of tumor size in some patients is suggestive of antitumor activity.

Journal Title: Archivum immunologiae et therapiae experimentalis

PUBMED ID: 18711186

DOI: doi.org/10.1200/JCO.2007.15.9970

Titolo: Predicting change in academic abilities after conformal radiation therapy for localized ependymoma.

Autori: Conklin HM., Li C., Xiong X., Ogg RJ., Merchant TE.

Data di Pubblicazione: 2008-8-20

Abstract: CRT may result in better long-term cognitive outcomes when compared to conventional radiation therapy approaches. Reading appears more vulnerable than other academic skills and may decline over time despite stable intellectual functioning.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 18676355

DOI: doi.org/10.1215/15228517-2008-058

Titolo: A novel tool to analyze MRI recurrence patterns in glioblastoma.

Autori: Wick W., Stupp R., Beule AC., Bromberg J., Wick A., Ernemann U., Platten M., Marosi C., Mason WP., van den Bent M., Weller M., Rorden C., Karnath HO., Karnath HO.

Data di Pubblicazione: 2008-8-5

Abstract: At least 10% of glioblastoma relapses occur at distant and even contralateral locations. This disseminated growth limits surgical intervention and contributes to neurological morbidity. Preclinical data pointed toward a role for temozolomide (TMZ) in reducing radiotherapy-induced glioma cell invasiveness. Our objective was to develop and validate a new analysis tool of MRI data to examine the clinical recurrence pattern of glioblastomas. MRICro software was used to map the location and extent of initial preoperative and recurrent tumors on MRI of 63 patients in the European Organisation for Research and Treatment of Cancer (EORTC) 26981/22981/National Cancer Institute of Canada (NCIC) CE.3 study into the same stereotaxic space. This allowed us to examine changes of site and distance between the initial and the recurrent tumor on the group level. Thirty of the 63 patients were treated using radiotherapy, while the other patients completed a radiotherapy-plus-TMZ treatment. Baseline characteristics (median age, KPS) and outcome data (progression-free survival, overall survival) of the patients included in this analysis resemble those of the general study cohort. The patient groups did not differ in the promoter methylation status of methyl guanine methyltransferase (MGMT). Overall frequency of distant recurrences was 20%. Analysis of recurrence patterns revealed no difference between the groups in the size of the recurrent tumor or in the differential effect on the distance of the recurrences from the preoperative tumor location. The data show the feasibility of groupwise recurrence pattern analysis. An effect of TMZ treatment on the recurrence pattern in the EORTC 26981/22981/NCIC CE.3 study could not be demonstrated.

Journal Title: Neuro-oncology

PUBMED ID: 18671639

DOI: doi.org/10.3171/JNS/2008/109/8/0268

Titolo: Bevacizumab and irinotecan therapy in glioblastoma multiforme: a series of 13 cases.

Autori: Ali SA., McHayleh WM., Ahmad A., Sehgal R., Braffet M., Rahman M., Bejjani G., Friedland DM.

Data di Pubblicazione: 2008-8-2

Abstract: The combination of bevacizumab and irinotecan is safe and has excellent activity even in this relapsed, heavily pretreated population of patients with high-grade malignant glioma, most of whom would not be candidates for clinical trials.

Journal Title: Journal of neurosurgery

PUBMED ID: 18632651

DOI: doi.org/10.1158/0008-5472.CAN-07-5973

Titolo: Vaccination elicits correlated immune and clinical responses in glioblastoma multiforme patients.

Autori: Wheeler CJ., Black KL., Liu G., Mazer M., Zhang XX., Pepkowitz S., Goldfinger D., Ng H., Irvin D., Yu JS.

Data di Pubblicazione: 2008-7-18

Abstract: Cancer vaccine trials have failed to yield robust immune-correlated clinical improvements as observed in animal models, fueling controversy over the utility of human cancer vaccines. Therapeutic vaccination represents an intriguing additional therapy for glioblastoma multiforme (GBM; grade 4 glioma), which has a dismal prognosis and treatment response, but only early phase I vaccine trial results have been reported. Immune and clinical responses from a phase II GBM vaccine trial are reported here. IFN-gamma responsiveness was quantified in peripheral blood of 32 GBM patients given therapeutic dendritic cell vaccines. Posttreatment times to tumor progression (TTP) and survival (TTS) were compared in vaccine responders and nonresponders and were correlated with immune response magnitudes. GBM patients (53%) exhibited  $\geq 1.5$ -fold vaccine-enhanced cytokine responses. Endogenous antitumor responses of similar magnitude occurred in 22% of GBM patients before vaccination. Vaccine responders exhibited significantly longer TTS and TTP relative to nonresponders. Immune enhancement in vaccine responders correlated logarithmically with TTS and TTP spanning postvaccine chemotherapy, but not with initial TTP spanning vaccination alone. This is the first report of a progressive correlation between cancer clinical outcome and T-cell responsiveness after therapeutic vaccination in humans and the first tracing of such correlation to therapeutically exploitable tumor alteration. As such, our findings offer unique opportunities to identify cellular and molecular components of clinically meaningful antitumor immunity in humans.

Journal Title: Cancer research

PUBMED ID: 18615600

DOI: doi.org/10.1002/cncr.23677

Titolo: Temozolomide for recurrent low-grade spinal cord gliomas in adults.

Autori: Chamberlain MC.

Data di Pubblicazione: 2008-7-11

Abstract: TMZ demonstrated modest efficacy with acceptable toxicity in this cohort of adult patients with recurrent low-grade spinal cord gliomas.

Journal Title: Cancer

PUBMED ID: 18602834

DOI: doi.org/10.1016/j.critrevonc.2008.05.005

Titolo: Treatment options for malignant gliomas, emphasizing towards new molecularly targeted therapies.

Autori: Argyriou AA., Antonacopoulou A., Iconomou G., Kalofonos HP.

Data di Pubblicazione: 2008-7-8

Abstract: Malignant gliomas (MGs), including glioblastomas and anaplastic astrocytomas are the most common primary brain tumors. Despite treatment advances, the outcome of patients diagnosed with MGs is poor. The current standard treatment protocols for managing these tumors include maximally safe surgical resection, followed by fractionated radiation therapy of the tumor and surrounding brain parenchyma. Until recently, the use of systemic chemotherapy was restricted and ineffective, due to the fact that the blood brain barrier inhibits the adequate therapeutic concentrations of most chemotherapeutic agents into the tumor and peritumoral area. Genetic transformation, like the expression of the DNA repair enzyme methylguanine methyltransferase (MGMT) and specific characteristics of these neoplasms are also causal factors, accounting for the development of treatment resistance to standard chemotherapy options with alkylating compounds. Recent advances, mostly, in thorough understanding of the complex molecular pathogenesis of MGs have led to arousal of rational development of new molecularly targeted treatment options that simultaneously affect multiple signalling pathways. Currently, several molecularly targeted agents, like tyrosine kinase and growth factor inhibitors have been tested in clinical trials to establish future directions in the therapy of MGs. A number of novel targeted strategies, including among others radio-immuno and ligand-toxin conjugates and RNA-based therapies, are also under investigation. We herein review and discuss the standard treatment options and recent advances in the therapy of MGs, with emphasis on the current knowledge towards the molecular pathogenesis of MGs as well as molecularly targeted therapies. We also highlight areas of future research.

Journal Title: Critical reviews in oncology/hematology

PUBMED ID: 18576918

DOI: doi.org/10.1089/hum.2008.035

Titolo: Toxicology study of repeat intracerebral administration of a measles virus derivative producing carcinoembryonic antigen in rhesus macaques in support of a phase I/II clinical trial for patients with recurrent gliomas.

Autori: Myers R., Harvey M., Kaufmann TJ., Greiner SM., Krempski JW., Raffel C., Shelton SE., Soeffker D., Zollman P., Federspiel MJ., Blanco M., Galanis E.

Data di Pubblicazione: 2008-6-26

Abstract: Gliomas have a dismal prognosis, with the median survival of patients with the most common histology, glioblastoma multiforme, being only 12-15 months. Development of novel therapeutic agents is urgently needed. We have previously demonstrated that oncolytic measles virus strains derived from the Edmonston vaccine lineage have significant antitumor activity against gliomas [Phuong, L.K., Allen, C., Peng, K.W., Giannini, C., Greiner, S., Teneyck, C.J., Mishra, P.K., Macura, S.I., Russell, S.J., Galanis, E.C. (2003). Cancer. Res. 63, 2462-2469]. MV-CEA is an Edmonston vaccine lineage measles virus strain engineered to express the marker peptide carcinoembryonic antigen (CEA): CEA levels can serve as a correlate of viral gene expression. In support of a phase I clinical trial of intratumoral and resection cavity administration of MV-CEA to patients with recurrent gliomas, we assessed the neurotoxicity of MV-CEA in adult immune male rhesus macaques (*Macaca mulatta*). The animals' immune status and administration schedule mimicked the trial population and proposed administration schema. *Macaca mulatta* represents the prototype animal species for assessment of measles neurotoxicity. The animals were stereotactically administered either vehicle (n = 1) or MV-CEA at  $2 \times 10^5$  or  $2 \times 10^6$  TCID<sub>50</sub> (each, n = 2) in the right frontal lobe in two injections on days 1 and 5. Macaques were closely monitored clinically for neurotoxicity. Body weight, temperature, complete blood count, CEA, clinical che

mistries, coagulation, complement levels, immunoglobulin, measles antibody titers, viremia, and shedding (buccal swabs) were tested at multiple time points. Furthermore, cisterna magna spinal taps were performed on day 9 and 1 year after the first viral dose administration, and samples were analyzed for protein, glucose, cell differential, and presence of MV-CEA. Magnetic resonance imaging (MRI) was performed between 4 and 5 months after article administration to assess for subclinical neurotoxicity. To date, 36+ months from study initiation there has been no clinical or biochemical evidence of toxicity, including lack of neurological symptoms, fever, or other systemic symptoms and lack of immunosuppression. Quantitative RT-PCR analysis of blood, buccal swabs, and cerebrospinal fluid (CSF) was negative for MV-CEA at all time points, with the exception of viral genome deletion in the blood of one asymptomatic animal at the  $2 \times 10^6$  TCID<sub>50</sub> dose level on day 85. Vero cell overlays of CSF cells and supernatant were negative for viral recovery. There was no detection of CEA in serum or CSF at any time point. MRI scans were negative for imaging abnormalities and showed no evidence of encephalitis. Our results support the safety of CNS administration of MV-CEA in glioma patients. A clinical trial of intratumoral and resection cavity administration of MV-CEA in patients with recurrent glioblastoma multiforme is currently ongoing.

Journal Title: Human gene therapy

PUBMED ID: 18521920

DOI: doi.org/10.1002/cncr.23585

Titolo: External beam irradiation and the combination of cisplatin and carmustine followed by carmustine alone for the treatment of high-grade glioma: a phase 2 Southwest Oncology Group trial.

Autori: Blumenthal DT., Rankin C., Eyre HJ., Livingston RB., Spence AM., Stelzer KJ., Rushing EJ., Berger MS., Rivkin SE., Cohn AL., Petersdorf SH.

Data di Pubblicazione: 2008-6-4

Abstract: Despite the presence of a cohort of long-term survivors, the results of the current study do not appear to support the additional study or routine use of concurrent cisplatin and carmustine.

Journal Title: Cancer

PUBMED ID: 18484645

DOI: doi.org/10.1002/cncr.23584

Titolo: Young age may predict a better outcome for children with diffuse pontine glioma.

Autori: Broniscer A., Laningham FH., Sanders RP., Kun LE., Ellison DW., Gajjar A.

Data di Pubblicazione: 2008-5-20

Abstract: Children aged <3 years with DPG potentially may fare better than older patients with the same diagnosis despite the use of similar therapy. The current results suggested that DPG in younger children may be distinct biologically from similar tumors in older age groups.

Journal Title: Cancer

PUBMED ID: 18484594

DOI: doi.org/10.1002/cncr.23562

Titolo: Incidence of early pseudo-progression in a cohort of malignant glioma patients treated with chemoradiation with temozolomide.

Autori: Taal W., Brandsma D., de Bruin HG., Bromberg JE., Swaak-Kragten AT., Smitt PA., van Es CA., van den Bent MJ.

Data di Pubblicazione: 2008-5-20

Abstract: Up to 50% of malignant glioma patients treated with RT/TMZ and progression immediately after RT develop pseudo-progression. The current study



data support the idea to continue TMZ in the case of progressive lesions immediately after RT/TMZ. Surgery should be considered in symptomatic cases. The inclusion of patients with progressive lesions developing directly after chemoradiation in studies regarding recurrent gliomas will lead to an overestimation of the results.

Journal Title: Cancer

PUBMED ID: 18483377

DOI: doi.org/10.1158/1078-0432.CCR-07-4875

Titolo: Postoperative adjuvant dendritic cell-based immunotherapy in patients with relapsed glioblastoma multiforme.

Autori: De Vleeschouwer S., Fieuws S., Rutkowski S., Van Calenbergh F., Van Loon J., Goffin J., Sciote R., Wilms G., Demaerel P., Warmuth-Metz M., Soerensen N., Wolff JE., Wagner S., Kaempgen E., Van Gool SW.

Data di Pubblicazione: 2008-5-17

Abstract: Adjuvant DC-based immunotherapy for patients with relapsed GBM is safe and can induce long-term survival. A trend to PFS improvement was shown in the faster vaccination schedule. The importance of age and a minimal residual disease status at the start of the vaccination is underscored.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 18480965

DOI: doi.org/10.1007/s11060-008-9613-6

Titolo: CPT-11 for recurrent temozolomide-refractory 1p19q co-deleted anaplastic oligodendroglioma.

Autori: Chamberlain MC., Glantz MJ.

Data di Pubblicazione: 2008-5-16

Abstract: CPT-11 demonstrated modest efficacy (similar to other salvage glioma regimens) with acceptable toxicity in this cohort of adults with recurrent, 1p19q co-deleted AO all of whom had failed prior TMZ chemotherapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 18461281

DOI: doi.org/10.1007/s11060-008-9607-4

Titolo: Radiochemotherapy with temozolomide as re-irradiation using high precision fractionated stereotactic radiotherapy (FSRT) in patients with recurrent gliomas.

Autori: Combs SE., Bischof M., Welzel T., Hof H., Oertel S., Debus J., Schulz-Ertner D.

Data di Pubblicazione: 2008-5-8

Abstract: Re-irradiation and TMZ is safe and effective in a subgroup of patients with recurrent gliomas. Further evaluation of radiochemotherapy regimen for recurrent or progressive gliomas is warranted.

Journal Title: Journal of neuro-oncology

PUBMED ID: 18452856

DOI: doi.org/10.1016/S1470-2045(08)70125-6

Titolo: Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas.

Autori: Brandsma D., Stalpers L., Taal W., Sminia P., van den Bent MJ.

Data di Pubblicazione: 2008-5-3

Abstract: Since the introduction of chemoradiotherapy with temozolomide as the new standard of care for patients with glioblastoma, there has been an increasing awareness of progressive and enhancing lesions on MRI, noted immediately after the end of treatment, which are not related to tumour progression.

n, but which are a treatment effect. This so-called pseudoprogression can occur in up to 20% of patients who have been treated with temozolomide chemoradiotherapy, and can explain about half of all cases of increasing lesions after the end of this treatment. These lesions decrease in size or stabilise without additional treatments and often remain clinically asymptomatic. Additionally, there is evidence that treatment-related necrosis occurs more frequently and earlier after temozolomide chemotherapy than after radiotherapy alone. The mechanisms behind these events have not yet been fully elucidated, but the likelihood is that chemoradiotherapy causes a higher degree of (desired) tumour-cell and endothelial-cell killing. This increased cell kill might lead to secondary reactions, such as oedema and abnormal vessel permeability in the tumour area, mimicking tumour progression, in addition to subsequent early treatment-related necrosis in some patients and milder subacute radiotherapy reactions in others. In patients managed with temozolomide chemoradiotherapy who have clinically asymptomatic progressive lesions at the end of treatment, adjuvant temozolomide should be continued; in clinically symptomatic patients, surgery should be considered. If mainly necrosis is noted during surgery, continuation of adjuvant temozolomide is logical. Trials on the treatment of recurrent malignant glioma should exclude patients with progression within the first 3 months after temozolomide chemoradiotherapy unless histological confirmation of tumour recurrence is available. Further research is needed to establish reliable imaging parameters that distinguish between true tumour progression and pseudoprogression or treatment-related necrosis.

Journal Title: The Lancet. Oncology

PUBMED ID: 18447714

DOI: doi.org/10.3171/JNS/2008/108/5/0963

Titolo: Phase II clinical trial of Wilms tumor 1 peptide vaccination for patients with recurrent glioblastoma multiforme.

Autori: Izumoto S., Tsuboi A., Oka Y., Suzuki T., Hashiba T., Kagawa N., Hashimoto N., Maruno M., Elisseeva OA., Shirakata T., Kawakami M., Oji Y., Nishida S., Ohno S., Kawase I., Hatazawa J., Nakatsuka S., Aozasa K., Morita S., Sakamoto J., Sugiyama H., Yoshimine T.

Data di Pubblicazione: 2008-5-2

Abstract: Although a small uncontrolled nonrandomized trial, this study showed that WT1 vaccine therapy for patients with WT1/HLA-A\*2402-positive recurrent GBM was safe and produced a clinical response. Based on these results, further clinical studies of WT1 vaccine therapy in patients with malignant glioma are warranted.

Journal Title: Journal of neurosurgery

PUBMED ID: 18403492

DOI: doi.org/10.1215/15228517-2008-005

Titolo: Phase II study of temozolomide, thalidomide, and celecoxib for newly diagnosed glioblastoma in adults.

Autori: Kesari S., Schiff D., Henson JW., Muzikansky A., Gigas DC., Doherty L., Batchelor TT., Longtine JA., Ligon KL., Weaver S., Laforme A., Ramakrishna N., Black PM., Drappatz J., Ciampa A., Folkman J., Kieran M., Wen PY.

Data di Pubblicazione: 2008-4-12

Abstract: We conducted a phase II study of the combination of temozolomide and angiogenesis inhibitors for treating adult patients with newly diagnosed glioblastoma. Patients who had stable disease following standard radiation therapy received temozolomide for 5 days in 28-day cycles, in combination with daily thalidomide and celecoxib. Patients were treated until tumor progression or development of unacceptable toxicity. Four-month progression-free survival (PFS) from study enrollment was the primary end point, and overall survival (OS) was the secondary end point. In addition, we sought to correlate

response with O(6)-methylguanine-DNA methyltransferase promoter methylation status and serum levels of angiogenic peptides. Fifty patients with glioblastoma were enrolled (18 women, 32 men). Median age was 54 years (range, 29-78) and median KPS score was 90 (range, 70-100). From study enrollment, median PFS was 5.9 months (95% confidence interval [CI]: 4.2-8.0) and 4-month PFS was 63% (95% CI: 46%-75%). Median OS was 12.6 months (95% CI: 8.5-16.4) and 1-year OS was 47%. Of the 47 patients evaluable for best response, none had a complete response, five (11%) had partial response, four (9%) had minor response, 22 (47%) had stable disease, and 16 (34%) had progressive disease. Analysis of serial serum samples obtained from 47 patients for four angiogenic peptides failed to show a significant correlation with response or survival for three of the peptides; higher vascular endothelial growth factor levels showed a trend toward correlation with decreased OS (p=0.07) and PFS (p=0.09). The addition of celecoxib and thalidomide to adjuvant temozolomide was well tolerated but did not meet the primary end point of improvement of 4-month PFS from study enrollment.

Journal Title: Neuro-oncology

PUBMED ID: 18362333

DOI: doi.org/10.1073/pnas.0801279105

Titolo: Identification of noninvasive imaging surrogates for brain tumor gene-expression modules.

Autori: Diehn M., Nardini C., Wang DS., McGovern S., Jayaraman M., Liang Y., Aldape K., Cha S., Kuo MD.

Data di Pubblicazione: 2008-3-26

Abstract: Glioblastoma multiforme (GBM) is the most common and lethal primary brain tumor in adults. We combined neuroimaging and DNA microarray analysis to create a multidimensional map of gene-expression patterns in GBM that provided clinically relevant insights into tumor biology. Tumor contrast enhancement and mass effect predicted activation of specific hypoxia and proliferation gene-expression programs, respectively. Overexpression of EGFR, a receptor tyrosine kinase and potential therapeutic target, was also directly inferred by neuroimaging and was validated in an independent set of tumors by immunohistochemistry. Furthermore, imaging provided insights into the intratumoral distribution of gene-expression patterns within GBM. Most notably, an "infiltrative" imaging phenotype was identified that predicted patient outcome. Patients with this imaging phenotype had a greater tendency toward having multiple tumor foci and demonstrated significantly shorter survival than their counterparts. Our findings provide an in vivo portrait of genome-wide gene expression in GBM and offer a potential strategy for noninvasively selecting patients who may be candidates for individualized therapies.

Journal Title: Proceedings of the National Academy of Sciences of the United States of America

PUBMED ID: 18361434

DOI: doi.org/10.1002/cncr.23404

Titolo: Salvage chemotherapy with CPT-11 for recurrent temozolomide-refractory anaplastic astrocytoma.

Autori: Chamberlain MC., Wei-Tsao DD., Blumenthal DT., Glantz MJ.

Data di Pubblicazione: 2008-3-26

Abstract: CPT-11 demonstrated modest efficacy with acceptable toxicity in this cohort of adult patients with recurrent AA, all of whom had failed on prior temozolomide chemotherapy.

Journal Title: Cancer

PUBMED ID: 18336940

DOI: doi.org/10.1016/j.radonc.2006.04.015

Titolo: Boron neutron capture therapy (BNCT) for glioblastoma multiforme: a phase II study evaluating a prolonged high-dose of boronophenylalanine (BPA)

Autori: Henriksson R., Capala J., Michanek A., Lindahl SA., Salford LG., Franzén L., Blomquist E., Westlin JE., Bergenheim AT., Bergenheim AT.

Data di Pubblicazione: 2008-3-14

Abstract: Although, the efficacy of BNCT in the present protocol seems to be comparable with conventional radiotherapy and the treatment time is shorter, the observed side effects and the requirement of complex infrastructure and higher resources emphasize the need of further phase I and II studies, especially directed to improve the accumulation of  $^{10}\text{B}$  in tumour cells.

Journal Title: Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology

PUBMED ID: 18301459

DOI: Mancante

Titolo: Pre-irradiation chemotherapy in high risk medulloblastoma.

Autori: Abd-El-Aal HH.

Data di Pubblicazione: 2008-2-28

Abstract: Pre-irradiation chemotherapy is effective in high risk medulloblastoma and is associated with acceptable side effects. The delay in craniospinal irradiation (CSI) for about 5 weeks to receive 2 courses of chemotherapy will not significantly increase disease progression. Multiple cycles of post-irradiation chemotherapy can be given safely after CSI. A larger number of patients and longer follow-up is needed to confirm the results.

Journal Title: Journal of the Egyptian National Cancer Institute

PUBMED ID: 18295834

DOI: doi.org/10.1016/j.surneu.2007.07.040

Titolo: Preliminary results from a phase I/II study of perillyl alcohol intranasal administration in adults with recurrent malignant gliomas.

Autori: da Fonseca CO., Schwartzmann G., Fischer J., Nagel J., Futuro D., Quirico-Santos T., Gattass CR.

Data di Pubblicazione: 2008-2-26

Abstract: There were no toxicity events. Perillyl alcohol is well tolerated and regression of tumor size in some patients is suggestive of antitumor activity. This work discusses POH intranasal delivery as a potential adjuvant therapeutic strategy for patients with malignant gliomas.

Journal Title: Surgical neurology

PUBMED ID: 18217208

DOI: doi.org/10.1007/s11060-008-9525-5

Titolo: Diffuse pontine gliomas in children: changing strategies, changing results? A mono-institutional 20-year experience.

Autori: Massimino M., Spreafico F., Biassoni V., Simonetti F., Riva D., Trecate G., Giombini S., Poggi G., Pecori E., Pignoli E., Casanova M., Ferrari A., Meazza C., Luksch R., Terenziani M., Cefalo G., Podda M., Polastri D., Clerici CA., Fossati-Bellani F., Gandola L.

Data di Pubblicazione: 2008-1-25

Abstract: Patients with diffuse pontine gliomas have a median survival of less than one year and represent a challenge for pediatric oncologists, prompting them to attempt experimental therapies. From 1987 to 2005, 62 children with diffuse pontine glioma, not amenable to curative surgery, were treated according to four successive pilot protocols: (1) concomitant chemo-radiotherapy (etoposide, cytarabine, ifosfamide, cisplatin, and dactinomycin); (2) intensive high-dose courses chemotherapy (cisplatin/etoposide, cyclophosphamide/vincristine/methotrexate) and a subsequent course of myeloablative thiop

a followed by radiation and maintenance chemotherapy; (3) cisplatin/etoposide followed by isotretinoin before, during and after focal irradiation; and (4) iv vinorelbine before, during, and after irradiation. Considering all patients, 77% experienced a transient response to treatment, always detectable after radiotherapy. The progression-free survival (PFS) rate was 25 +/- 6% at one year, median PFS was seven months; overall survival (OS) was 45 +/- 6%, median OS was eleven months: no statistical differences in the four studies in terms of outcome were detected. Despite improved diagnostic, therapeutic, and supportive tools in pediatric neuro-oncology, little has been achieved for patients with diffuse pontine tumors.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 21892317  
DOI: doi.org/10.4137/cmo.s827  
Titolo: A Single Institution's Experience with Bevacizumab in Combination with Cytotoxic Chemotherapy in Progressive Malignant Glioma.  
Autori: Mayer T., Lacy J., Baehring J.  
Data di Pubblicazione: 2011-9-6  
Abstract: Overall, our results confirm the efficacy and safety of bevacizumab in combination with chemotherapy in patients with progressive malignant glioma. Although the TTF and OS were less than previously reported with the combination of bevacizumab and irinotecan, this was an unselected patient population with 50% of patients having received >1 prior chemotherapy regimen.  
Journal Title: Clinical medicine. Oncology

PUBMED ID: 18157537  
DOI: doi.org/10.1007/s00381-007-0565-5  
Titolo: Assessment of chemotherapeutic response in children with proptosis due to optic nerve glioma.  
Autori: Diaz RJ., Laughlin S., Nicolin G., Buncic JR., Bouffet E., Bartels U.  
Data di Pubblicazione: 2007-12-25  
Abstract: We have found that a proptosis index <1 correlates with a chemotherapeutic maintained response and an index >1 correlates with progressive disease.  
Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 18079578  
DOI: doi.org/10.4103/0973-1482.37408  
Titolo: Synchronous dual malignancy: successfully treated cases.  
Autori: Agrawal R.  
Data di Pubblicazione: 2007-12-15  
Abstract: The occurrence of a second malignancy in a patient with a known malignant tumour is not uncommon. Synchronous primary malignancies are still unusual. We are presenting two cases treated successfully at our centre. Case report 1-A 70 year old female presented to us with lump in right breast for two years and bleeding per vaginum for two years. Histopathology of cervix showed squamous cell carcinoma (large cell non keratinizing) and clinical stage was IIIB. HPE mastectomy specimen showed infiltrating duct carcinoma and stage II. Patient was treated with external beam radiotherapy for carcinoma cervix and breast simultaneously and chemotherapy as required. Patient is on regular follow up and clinically no evidence of disease. Case Report 2 -A 40 year old female presented with mild headache off and on for one year, projectile vomiting for three months and right side facial swelling for three months. HPE brain tissue showed astrocytoma grade II and HPE parotid tumour showed low grade muco-epidermoid carcinoma. Patient was treated with surgery first.

st then radiotherapy. Patient is in regular follow up, having no complain, clinically no neurological dysfunction and no evidence of disease at right parotid and neck region. Thus it was concluded that patients responded well to treatment. Treatment strategies in case of synchronous double malignancy depend on treating the malignancy that is more advanced first or sometimes both could be treated simultaneously. In our case we concluded that synchronous double malignancy may be treated successfully. Both sites should be treated fully as if they were occurring separately considering toxicities.

Journal Title: Journal of cancer research and therapeutics

PUBMED ID: 18031705

DOI: doi.org/10.1016/S1474-4422(07)70289-2

Titolo: Medulloblastoma in childhood: new biological advances.

Autori: Crawford JR., MacDonald TJ., Packer RJ.

Data di Pubblicazione: 2007-11-23

Abstract: Medulloblastoma is the most common embryonal tumour in children. Patients with medulloblastoma are currently staged as average-risk or poor-risk on the basis of clinical findings. With current multimodality therapy, nearly 90% of children with average-risk, non-disseminated medulloblastoma have 5-year event-free survival, and those with high-risk disease have a 60-65% survival rate; however, the outcome for younger children, particularly infants, is worse. Children who survive medulloblastoma are at risk of long-term sequelae related to the neurological effects of the tumour, surgery, or radiotherapy, and the additive effects of chemotherapy. Molecular biology has changed our understanding of medulloblastoma and has implications for diagnostic stratification and treatment. As newer biological agents are translated from the lab to the bedside, clinicians need to understand the fundamental signalling pathways that are targeted during therapy. Greater understanding of the molecular biology of medulloblastoma is needed so that more children can be cured or have an improved quality of life.

Journal Title: The Lancet. Neurology

PUBMED ID: 17941492

DOI: doi.org/10.3171/PED-07/10/286

Titolo: Pediatric infratentorial gangliogliomas: a retrospective series.

Autori: Baussard B., Di Rocco F., Garnett MR., Boddaert N., Lellouch-Tubiana A., Grill J., Puget S., Roujeau T., Zerah M., Sainte-Rose C.

Data di Pubblicazione: 2007-10-19

Abstract: The imaging of gangliogliomas in the posterior fossa showed patchy enhancement. The patients in whom it was possible to achieve a radical resection, aimed at removing at least the enhancing portion of the tumor, have not required further treatment. A second excision, for progressive tumors, is an effective adjuvant therapy.

Journal Title: Journal of neurosurgery

PUBMED ID: 17941070

DOI: doi.org/10.1002/pbc.21381

Titolo: Feasibility of metronomic maintenance chemotherapy following high-dose chemotherapy for malignant central nervous system tumors.

Autori: Choi LM., Rood B., Kamani N., La Fond D., Packer RJ., Santi MR., MacDonald TJ.

Data di Pubblicazione: 2007-10-18

Abstract: Metronomic chemotherapy in this patient population is feasible and shows encouraging preliminary results, especially in patients with metastatic disease who have not received craniospinal radiation. Further investigation of this strategy in newly diagnosed patients with CNS tumors is warranted.

Journal Title: Pediatric blood & cancer

PUBMED ID: 17932894

DOI: doi.org/10.1002/cncr.23078

Titolo: A phase II study of the farnesyl transferase inhibitor, tipifarnib, in children with recurrent or progressive high-grade glioma, medulloblastoma/primitive neuroectodermal tumor, or brainstem glioma: a Children's Oncology Group study.

Autori: Fouladi M., Nicholson HS., Zhou T., Laningham F., Helton KJ., Holmes E., Cohen K., Speights RA., Wright J., Pollack IF., Pollack IF.

Data di Pubblicazione: 2007-10-13

Abstract: Tipifarnib tolerated well but had little activity as a single agent in children with recurrent central nervous system malignancies.

Journal Title: Cancer

PUBMED ID: 17906461

DOI: doi.org/10.1097/CCO.0b013e3282f03152

Titolo: Recent development in chemotherapy of paediatric brain tumours.

Autori: Grill J., Bhangoo R.

Data di Pubblicazione: 2007-10-2

Abstract: In the most frequent paediatric brain tumors (medulloblastoma and low grade gliomas), the improvements have been impressive in recent years. These patients still await new targeted therapies to lower the burden of treatments and their related side-effects. Most of the brain tumours, however, are rare and the development of specific protocols too slow. Likely, they may have very specific biologic abnormalities that could be efficiently targeted in the near future.

Journal Title: Current opinion in oncology

PUBMED ID: 17805033

DOI: doi.org/10.1097/MPH.0b013e318142b585

Titolo: A phase 2 feasibility study of sequential, dose intensive chemotherapy to treat progressive low-grade gliomas in children.

Autori: Bruggers CS., Greene D.

Data di Pubblicazione: 2007-9-7

Abstract: Administration of sequential, dose intense chemotherapy was feasible and clinically tolerated. Concurrent anticonvulsant therapy limited dose intensity in 2 patients. Although efficacy appeared consistent with published larger series, small patient number in this study precludes definitive conclusions.

Journal Title: Journal of pediatric hematology/oncology

PUBMED ID: 17704361

DOI: doi.org/10.1215/15228517-2007-031

Titolo: Visual outcome of a cohort of children with neurofibromatosis type 1 and optic pathway glioma followed by a pediatric neuro-oncology program.

Autori: Dalla Via P., Opocher E., Pinello ML., Calderone M., Viscardi E., Clementi M., Battistella PA., Laverda AM., Da Dalt L., Perilongo G.

Data di Pubblicazione: 2007-8-21

Abstract: We evaluated the visual outcome of a cohort of children with neurofibromatosis type 1 (NF1) and optic pathway glioma (OPG) treated according to standardized therapeutic guidelines. The study population consisted of all consecutive patients with NF1 and OPG referred to a specialized pediatric neuro-oncology program between 1994 and 2004. Treatment was instituted only in cases of progressive disease or clinical deterioration. Treatment modalities were chemotherapy (based on vincristine/carboplatin) for children younger than 5 years and radiotherapy for all others. Ten boys and 10 girls (seven with

h a positive family history) entered the trial (median age at diagnosis of OPG, 29 months). At a median follow-up time of 78 months, seven patients had been treated with chemotherapy only, four with radiotherapy, and four with chemotherapy plus radiotherapy. Five patients were observed only. Currently, 18 are alive and two have died. Eight patients were treated for progressive visual loss in the face of stable disease, five for tumor volume increase without visual deterioration, and two for symptomatic tumor volume increase. At referral, six children had a visual acuity (VA) of < 30% in both eyes; eight children had 100% VA bilaterally. At referral, the visual field (VF) could be assessed in three children: One had VF loss in both eyes, one had VF loss in one eye, and one had normal VF. At last follow-up, eight children had VA < 20% in both eyes; only two children had 100% VA in both eyes. Among 11 children who had some visual function, three had VF loss in one eye and three in both eyes, and five had an intact VF. Contrast and color sensitivity were abnormal in seven and six patients, respectively. Thirteen children fell into the WHO hypovision category. In summary, among the 15 children treated, one had a definitive and two a mild improvement in VA. In conclusion, the visual outcome of this selected cohort of NF1 patients with OPG is unsatisfactory. A critical reappraisal of the therapeutic strategy adopted is needed.  
Journal Title: Neuro-oncology

PUBMED ID: 17679463

DOI: Mancante

Titolo: Epidermal growth factor receptor serum levels and prognostic value in malignant gliomas.

Autori: Quaranta M., Divella R., Daniele A., Di Tardo S., Venneri MT., Lolli I., Troccoli G.

Data di Pubblicazione: 2007-8-8

Abstract: Although a prospective study with large sample size is warranted, serum EGFR extracellular domain may be potentially useful as a biological marker of gliomas for prediction of prognosis and follow-up after treatment.

Journal Title: Tumori

PUBMED ID: 17641821

DOI: doi.org/10.1007/s11060-007-9444-x

Titolo: Pegylated-liposomal doxorubicin and oral topotecan in eight children with relapsed high-grade malignant brain tumors.

Autori: Wagner S., Peters O., Fels C., Janssen G., Liebeskind AK., Sauerbrey A., Suttorp M., Hau P., Wolff JE.

Data di Pubblicazione: 2007-7-21

Abstract: The schedule of PEG-liposomal doxorubicin with 30-40 mg/m<sup>2</sup> every 4 weeks in combination with oral topotecan resulted in tumor response, but the toxicity was high. An individualized increasing dose of PEG-liposomal doxorubicin 10-20 mg/m<sup>2</sup> every two weeks is now recommended.

Journal Title: Journal of neuro-oncology

PUBMED ID: 17634493

DOI: doi.org/10.1200/JCO.2006.09.4243

Titolo: Phase I and pharmacokinetic study of the oral farnesyltransferase inhibitor lonafarnib administered twice daily to pediatric patients with advanced central nervous system tumors using a modified continuous reassessment method: a Pediatric Brain Tumor Consortium Study.

Autori: Kieran MW., Packer RJ., Onar A., Blaney SM., Phillips P., Pollack IF., Geyer JR., Gururangan S., Banerjee A., Goldman S., Turner CD., Belasco JB., Broniscer A., Zhu Y., Frank E., Kirschmeier P., Statkevich P., Yver A., Boyett JM., Kun LE.

Data di Pubblicazione: 2007-7-20



Abstract: Although the estimated MTD by the CRM model was 98.5 mg/m<sup>2</sup>/dose, because of the relatively constant observed DLT rate at the lower four dose levels, the recommended phase II dose of lonafarnib is 115 mg/m<sup>2</sup>/dose administered twice daily by mouth with concurrent loperamide.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 17628746

DOI: doi.org/10.1007/s11060-007-9459-3

Titolo: Primary diffuse leptomeningeal gliosarcomatosis.

Autori: Watanabe Y., Hotta T., Yoshioka H., Itou Y., Taniyama K., Sugiyama K.

Data di Pubblicazione: 2007-7-14

Abstract: We report a 48-year-old woman with primary diffuse leptomeningeal gliomatosis (PDLG) histologically diagnosed as gliosarcoma. She was admitted complaining of headache, numbness of the right arm, double vision, and visual field defects. Computerized tomography (CT) scans showed ventricular dilatation consistent with communicating hydrocephalus. Magnetic resonance imaging (MRI) revealed diffuse meningeal thickening and gadolinium enhancement without a definite intraparenchymal lesion. Whole-spine MRI demonstrated across-the-board dural thickening and gadolinium enhancement. Cytological examination showed atypical anaplastic cells. As no diagnosis could be made she underwent biopsy of the leptomeninges. Histological examination of the specimen returned a diagnosis of gliosarcoma. Despite chemotherapy and radiotherapy she died 11 months after admission. Autopsy findings included gliosarcoma in the leptomeninges and spinal cord without an underlying parenchymal tumor. To our knowledge, this is the first report of primary diffuse leptomeningeal gliosarcomatosis.

Journal Title: Journal of neuro-oncology

PUBMED ID: 17594055

DOI: doi.org/10.1007/s11060-007-9408-1

Titolo: Myelosuppression in patients benefiting from imatinib with hydroxyurea for recurrent malignant gliomas.

Autori: Shah GD., Silver JS., Rosenfeld SS., Gavrilovic IT., Abrey LE., Lassman AB.

Data di Pubblicazione: 2007-6-28

Abstract: Reports suggest reasonable efficacy and minimal myelosuppression from combination imatinib and hydroxyurea for recurrent malignant glioma. We retrospectively reviewed 16 patients treated with this regimen who were evaluable for toxicity; 14 were also evaluable for response. The incidence of grade 3-4 hematologic toxicity was 25%. The best radiographic response, by MacDonald criteria, was partial response (PR) in three patients (21%), stable disease (SD) in four (29%), and progressive disease (PD) in seven (50%). One patient with a PR developed therapy-limiting hematologic toxicity on day 19 of treatment, progressing to grade 4 on day 64, and persisting until death on day 127 despite discontinuing both drugs. Another patient with PR and two of four patients with SD also developed grade 3 hematologic toxicity. All patients with grade 3-4 hematologic toxicity had disease control (PR or SD) as best radiographic response, whereas none with PD suffered grade 3-4 hematologic toxicity. Combining imatinib with hydroxyurea is effective in some patients with malignant glioma. However, myelosuppression can persist for months after discontinuing the regimen, precluding further chemotherapy. Disease control may also correlate with hematologic toxicity ( $p = 0.08$ ), suggesting that glioma and marrow stem cells may share a common sensitivity to this chemotherapy regimen.

Journal Title: Journal of neuro-oncology

PUBMED ID: 17576523

DOI: doi.org/10.1007/s11060-007-9427-y

Titolo: Salvage chemotherapy with procarbazine and fotemustine combination in the treatment of temozolomide treated recurrent glioblastoma patients.

Autori: Silvani A., Lamperti E., Gaviani P., Eoli M., Fiumani A., Salmaggi A., Falcone C., Filippini G., Botturi A., Boiardi A.

Data di Pubblicazione: 2007-6-20

Abstract: The purpose of this study was to evaluate safety and efficacy of Procarbazine (PCB) and fotemustine (FTM) combination in the treatment of pre-temozolomide treated, recurrent GBM patients. The primary end-point was progression free survival at 6 months (PFS-6). Secondary end-points were overall survival, response rates (CR + PR) and toxicity. About 54 patients (41 men and 13 women) aged 26-68 years (median age, 53.5 years) with recurrent GBM were treated. PCB was administered as an oral dosage of 450 mg on days 1-2 and a total dose of 300 mg on day 3. FTM was administered on day 3, 3 h after the last PCB intake at a dose of 110 mg/mq/BSA. The treatment was repeated every 5 weeks. Treatment was continued for a maximum of six cycles or until disease progression. After two cycles of chemotherapy: 6 patients (11.2%) experienced a neuroradiographic partial response (PR), 29 patients (53.7%) had stable disease (SD), and 19 patients (35.1%) had progressive disease (PD). For the whole group of patients, the median PFS was 19.3 weeks (95% CI, 14.1-24.4 weeks), and PFS-6 was 26.7% (95% CI, 10.6-42.8%). Overall MST from the beginning of PCB + FTM chemotherapy was 28.7 weeks (95% CI, 24.8-32.7 weeks). At 6 and 12 months, 64.4% (95% CI, 51.5-77.3%) and 23.6% (95% CI, 10.1-37.1%) of patients were alive. The median survival time calculated from the first diagnosis was 20.8 months (95% CI, 16.7-24.8). We concluded that the PCB + FTM combination as done in the current trial for patients with recurrent GBM after treatment with TMZ showed some benefit with regards to increased survival and that a Phase III trial is warranted.

Journal Title: Journal of neuro-oncology

PUBMED ID: 17553214

DOI: doi.org/10.1179/016164107X208068

Titolo: Loss of heterozygosity analysis in an anaplastic oligodendroglioma arising after radiation therapy.

Autori: Hata N., Shono T., Mizoguchi M., Matsumoto K., Guan Y., Nagata S., Hayashi K., Iwaki T., Sasaki T.

Data di Pubblicazione: 2007-6-8

Abstract: The anaplastic oligodendroglioma presented in this report showed a more aggressive clinical course than was expected from the genetic analysis. The significance of 1p and 19q LOH in radiation-induced oligodendroglial tumors might differ from that in spontaneous counterparts.

Journal Title: Neurological research

PUBMED ID: 17551011

DOI: doi.org/10.1073/pnas.0702916104

Titolo: Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors.

Autori: Kirson ED., Dbalý V., Tovarys F., Vymazal J., Soustiel JF., Itzhaki A., Mordechovich D., Steinberg-Shapira S., Gurvich Z., Schneiderman R., Wasserman Y., Salzberg M., Ryffel B., Goldsher D., Dekel E., Palti Y.

Data di Pubblicazione: 2007-6-7

Abstract: We have recently shown that low intensity, intermediate frequency, electric fields inhibit by an anti-microtubule mechanism of action, cancerous cell growth in vitro. Using implanted electrodes, these fields were also shown to inhibit the growth of dermal tumors in mice. The present study extends these findings to additional cell lines [human breast carcinoma; MDA-MB-2

31, and human non-small-cell lung carcinoma (H1299)] and to animal tumor models (intradermal B16F1 melanoma and intracranial F-98 glioma) using external insulated electrodes. These findings led to the initiation of a pilot clinical trial of the effects of TTFields in 10 patients with recurrent glioblastoma (GBM). Median time to disease progression in these patients was 26.1 weeks and median overall survival was 62.2 weeks. These time to disease progression and OS values are more than double the reported medians of historical control patients. No device-related serious adverse events were seen after >70 months of cumulative treatment in all of the patients. The only device-related side effect seen was a mild to moderate contact dermatitis beneath the field delivering electrodes. We conclude that TTFields are a safe and effective new treatment modality which effectively slows down tumor growth in vitro, in vivo and, as demonstrated here, in human cancer patients.

Journal Title: Proceedings of the National Academy of Sciences of the United States of America

PUBMED ID: 17517052

DOI: doi.org/10.1111/j.1349-7006.2007.00518.x

Titolo: Clinical trial of autologous formalin-fixed tumor vaccine for glioblastoma multiforme patients.

Autori: Ishikawa E., Tsuboi K., Yamamoto T., Muroi A., Takano S., Enomoto T., Matsumura A., Ohno T.

Data di Pubblicazione: 2007-5-23

Abstract: A pilot study was performed to investigate the safety and feasibility of autologous formalin-fixed tumor vaccines (AFTV) and the clinical responses to these vaccines by glioblastoma multiforme (GBM) patients. Twelve primary GBM patients were recruited. Eight had recurrent disease while four had been treated for primary disease but retained a visible tumor mass. AFTV were prepared from formalin-fixed and/or paraffin-embedded tumor tissue obtained upon surgery and premixed with original adjuvant materials. The patients were given three five-site intradermal inoculations at weekly intervals. A delayed-type hypersensitivity test was performed before and after each vaccination. In addition, the tumor tissues were subjected to immunohistochemical analysis to determine whether MIB-1, p53, and major histocompatibility complex (MHC) class-I complex expression could predict the response to the treatment. The treatment was well tolerated, with only local erythema, induration, and low-grade fever being reported. Of the 12 patients, one showed a complete response, one showed a partial response, two showed minor responses, one had stable disease, and seven exhibited progressive disease. The median survival period was 10.7 months from the initiation of the AFTV treatment but three of the five responders survived for 20 months or more after AFTV inoculation. Low p53 and high MHC class-I expression by the tumor may help predict the efficacy of this therapy. Thus, the AFTV is safe and feasible, and could significantly improve the outcome of GBM. Further clinical investigations to confirm this are highly desirable.

Journal Title: Cancer science

PUBMED ID: 17515545

DOI: doi.org/10.1212/01.wnl.0000262034.26310.a2

Titolo: Temozolomide for low-grade gliomas: predictive impact of 1p/19q loss on response and outcome.

Autori: Kaloshi G., Benouaich-Amiel A., Diakite F., Taillibert S., Lejeune J., Laigle-Donadey F., Renard MA., Iraqi W., Idbaih A., Paris S., Capelle L., Duffau H., Cornu P., Simon JM., Mokhtari K., Polivka M., Omuro A., Carpentier A., Sanson M., Delattre JY., Hoang-Xuan K.

Data di Pubblicazione: 2007-5-23

Abstract: Low-grade gliomas respond to temozolomide and loss of chromosome 1p/19q predicts both a durable chemosensitivity and a favorable outcome.

Journal Title: Neurology

PUBMED ID: 17452651

DOI: doi.org/10.1215/15228517-2007-006

Titolo: Phase II study of metronomic chemotherapy for recurrent malignant gliomas in adults.

Autori: Kesari S., Schiff D., Doherty L., Gigas DC., Batchelor TT., Muzikansky A., O'Neill A., Drappatz J., Chen-Plotkin AS., Ramakrishna N., Weiss SE., Levy B., Bradshaw J., Kracher J., Laforme A., Black PM., Folkman J., Kieran M., Wen PY.

Data di Pubblicazione: 2007-4-25

Abstract: Preclinical evidence suggests that continuous low-dose daily (metronomic) chemotherapy may inhibit tumor endothelial cell proliferation (angiogenesis) and prevent tumor growth. This phase II study evaluated the feasibility of this antiangiogenic chemotherapy regimen in adults with recurrent malignant gliomas. The regimen consisted of low-dose etoposide (35 mg/m<sup>2</sup> [maximum, 100 mg/day] daily for 21 days), alternating every 21 days with cyclophosphamide (2 mg/kg [maximum, 100 mg/day] daily for 21 days), in combination with daily thalidomide and celecoxib, in adult patients with recurrent malignant gliomas. Serum and urine samples were collected for measurement of angiogenic peptides. Forty-eight patients were enrolled (15 female, 33 male). Twenty-eight patients had glioblastoma multiforme (GBMs), and 20 had anaplastic gliomas (AGs). Median age was 53 years (range, 33-74 years), and median KPS was 70 (range, 60-100). Therapy was reasonably well tolerated in this heavily pretreated population. Two percent of patients had partial response, 9% had a minor response, 59% had stable disease, and 30% had progressive disease. For GBM patients, median progression-free survival (PFS) was 11 weeks, six-month PFS (6M-PFS) was 9%, and median overall survival (OS) was 21 weeks. For AG patients, median PFS was 14 weeks, 6M-PFS was 26%, and median OS was 41.5 weeks. In a limited subset of patients, serum and urine angiogenic peptides did not correlate with response or survival ( $p > 0.05$ ). Although there were some responders, this four-drug, oral metronomic regimen did not significantly improve OS in this heavily pretreated group of patients who were generally not eligible for conventional protocols. While metronomic chemotherapy may not be useful in patients with advanced disease, further studies using metronomic chemotherapy combined with more potent antiangiogenic agents in patients with less advanced disease may be warranted.

Journal Title: Neuro-oncology

PUBMED ID: 17442989

DOI: doi.org/10.1200/JCO.2006.07.4807

Titolo: Correlation between O6-methylguanine-DNA methyltransferase and survival in inoperable newly diagnosed glioblastoma patients treated with neoadjuvant temozolomide.

Autori: Chinot OL., Barrié M., Fuentes S., Eudes N., Lancelot S., Metellus P., Muracciole X., Braguer D., Ouafik L., Martin PM., Dufour H., Figarella-Branger D.

Data di Pubblicazione: 2007-4-20

Abstract: This dose-dense temozolomide regimen resulted in modest antitumor activity with an acceptable safety profile in the neoadjuvant setting, and expression of MGMT correlated with response to temozolomide. However, this treatment approach seems to be inferior to standard concomitant RT plus temozolomide.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 17431544

DOI: doi.org/10.1007/s11060-007-9370-y

Titolo: Prognosis in patients with anaplastic oligoastrocytoma is associated with histologic grade.

Autori: Buckner JC., O'Fallon JR., Dinapoli RP., Schomberg PJ., Farr G., Schaefer P., Giannini C., Scheithauer BW., Ballman KV.

Data di Pubblicazione: 2007-4-14

Abstract: Patients with anaplastic oligoastrocytoma have distinct outcomes based upon grade (OA3 vs. OA4) and in comparison with pure astrocytoma (AA or GBM). Future trials which include more than one histologic entity need to report results by cell type and grade and account for the varying prognoses in interpreting treatment outcomes.

Journal Title: Journal of neuro-oncology

PUBMED ID: 17401087

DOI: doi.org/10.2967/jnumed.106.037895

Titolo: Prognostic value of O-(2-18F-fluoroethyl)-L-tyrosine PET and MRI in low-grade glioma.

Autori: Floeth FW., Pauleit D., Sabel M., Stoffels G., Reifenberger G., Riemschneider MJ., Jansen P., Coenen HH., Steiger HJ., Langen KJ.

Data di Pubblicazione: 2007-4-3

Abstract: We conclude that baseline amino acid uptake on (18)F-FET PET and a diffuse versus circumscribed tumor pattern on MRI are strong predictors for the outcome of patients with low-grade glioma.

Journal Title: Journal of nuclear medicine : official publication, Society of Nuclear Medicine

PUBMED ID: 17393043

DOI: doi.org/10.1016/s1130-1473(07)70305-6

Titolo: Cerebral blood flow increase in cancer patients by applying cervical spinal cord stimulation.

Autori: Clavo B., Robaina F., Catalá L., Lloret M., Pinar B., Caramés MA., Ruiz A., Cabezón A., González G., Lara P., Ruiz-Egea E., Hernández MA.

Data di Pubblicazione: 2007-3-30

Abstract: The results suggest that neuro-stimulation spinal cord electrical stimulation can increase cerebral blood flow in cancer patients. The implication is that this technique could be useful in modifying locoregional ischemia in brain tumors thus improving the outcomes of after radio-chemotherapy. Further research is in progress to confirm the advantages of the technique.

Journal Title: Neurocirugia (Asturias, Spain)

PUBMED ID: 17388696

DOI: doi.org/10.1667/RR0725.1

Titolo: Image fusion analysis of volumetric changes after interstitial low-dose-rate iodine-125 irradiation of supratentorial low-grade gliomas.

Autori: Julow J., Major T., Mangel L., Bajzik G., Viola A.

Data di Pubblicazione: 2007-3-29

Abstract: The aim of this study was to compare the volumes of tumor necrosis, reactive zone and edema with the three-dimensional dose distributions after brachytherapy treatments of gliomas. The investigation was performed an average of 14.2 months after low-dose-rate (125)I interstitial irradiation of 25 inoperable low-grade gliomas. The prescribed dose was 50-60 Gy to the tumor surface. Dose planning and image fusion were performed with the BrainLab-Target 1.19 software. In the CT/ MRI images, the "triple ring" (tumor necrosis, reactive ring and edema) developing after the interstitial irradiation of the brain tumors was examined. The images with the triple ring were fused with the planning images, and the isodose curves were superimposed on them. The volumes of the three regions were measured. The average dose at the necr

osis border was determined from the isodose distribution. For quantitative assessment of the dose distributions, the dose nonuniformity ratio (DNR), homogeneity index (HI), coverage index (CI) and conformal index (COIN) were calculated. The relative volumes of the different parts of the triple ring after the interstitial irradiation compared to the reference dose volume were the following: necrosis, 40.9%, reactive zone, 47.1%, and edema, 367%. The tumor necrosis developed at 79.1 Gy on average. The average DNR, HI, CI and COIN were 0.45, 0.24, 0.94 and 0.57, respectively. The image fusion analysis of the volume of tumor necrosis, reactive ring and edema caused by interstitial irradiation and their correlation with the dose distribution provide valuable information for patient follow-up, treatment options, and effects and side effects of radio therapy.

Journal Title: Radiation research

PUBMED ID: 17353924

DOI: doi.org/10.1038/sj.bjc.6603669

Titolo: Gefitinib in patients with progressive high-grade gliomas: a multicentre phase II study by Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO).

Autori: Franceschi E., Cavallo G., Lonardi S., Magrini E., Tosoni A., Grosso D., Scopece L., Blatt V., Urbini B., Pession A., Tallini G., Crinò L., Brandes AA.

Data di Pubblicazione: 2007-3-14

Abstract: To investigate the role of gefitinib in patients with high-grade gliomas (HGGs), a phase II trial (1839IL/0116) was conducted in patients with disease recurrence following surgery plus radiotherapy and first-line chemotherapy. Adult patients with histologically confirmed recurrent HGGs following surgery, radiotherapy and first-line chemotherapy, were considered eligible. Patients were treated with gefitinib (250 mg day<sup>-1</sup>) continuously until disease progression. The primary end point was progression-free survival at 6 months progression-free survival at 6 months (PFS-6). Tissue biomarkers (epidermal growth factor receptor (EGFR) gene status and expression, phosphorylated Akt (p-Akt) expression) were assessed. Twenty-eight patients (median age, 55 years; median ECOG performance status, 1) were enrolled; all were evaluable for drug activity and safety. Sixteen patients had glioblastoma, three patients had anaplastic oligodendrogliomas and nine patients had anaplastic astrocytoma. Five patients (17.9%, 95% CI 6.1-36.9%) showed disease stabilisation. The overall median time to progression was 8.4 (range 2-104+) weeks and PFS-6 was 14.3% (95% CI 4.0-32.7%). The median overall survival was 24.6 weeks (range 4-104+). No grade 3-4 gefitinib-related toxicity was found. Gefitinib showed limited activity in patients affected by HGGs. Epidermal growth factor receptor expression or gene status, and p-Akt expression do not seem to predict activity of this drug.

Journal Title: British journal of cancer

PUBMED ID: 17347491

DOI: doi.org/10.1215/15228517-2006-030

Titolo: Temozolomide in children with progressive low-grade glioma.

Autori: Gururangan S., Fisher MJ., Allen JC., Herndon JE., Quinn JA., Reardon DA., Vredenburgh JJ., Desjardins A., Phillips PC., Watral MA., Krauser JM., Friedman AH., Friedman HS.

Data di Pubblicazione: 2007-3-10

Abstract: We conducted a phase II study to assess the efficacy of oral temozolomide (TMZ) in children with progressive low-grade glioma. Thirty eligible patients were enrolled on this study. Median age at enrollment was 10 years (range, 4-18 years). Eligible patients received TMZ (200 mg/m<sup>2</sup> per day) by mouth for five days every four weeks. Patients received a median of nine cycles (range, 2-12 cycles) of treatment. Best responses in the 26 patients (86

%) with optic pathway glioma (OPG)/pilocytic astrocytoma (PA) included partial response in 3 patients (11%), minor response in 1 (4%), stable disease in 10 (38%), and progressive disease in 12 (46%). Only one of four patients with fibrillary astrocytoma had stable disease for 29 months after TMZ. The overall disease stabilization rate in patients with OPG/PA was 54%, and disease control was maintained for a median interval of 34 months. Seventeen of 26 patients had progressive disease either on or off therapy, and three have died of disease. The two-year progression-free and overall survivals in patients with OPG/PA were 49% (95% CI, 30%-67%) and 96% (95% CI, 89%-100%), respectively. Worst toxicity related to TMZ in all 30 patients included grade 2-4 thrombocytopenia in seven patients, grade 2-4 neutropenia in seven, grade 2 skin rash in one, and intratumor hemorrhage in one. TMZ given in this schedule was successful in stabilizing disease in a significant proportion of the patients with OPG/PA, with manageable toxicity.

Journal Title: Neuro-oncology

PUBMED ID: 17278121

DOI: doi.org/10.1002/pbc.21154

Titolo: Treatment of children with diffuse intrinsic brain stem glioma with radiotherapy, vincristine and oral VP-16: a Children's Oncology Group phase II study.

Autori: Korones DN., Fisher PG., Kretschmar C., Zhou T., Chen Z., Kepner J., Freeman C.

Data di Pubblicazione: 2007-2-6

Abstract: The addition of vincristine and oral VP-16 to standard external beam radiation causes moderate toxicity and does not improve survival of children with diffuse intrinsic brain stem glioma.

Journal Title: Pediatric blood & cancer

PUBMED ID: 17245623

DOI: doi.org/10.1007/s11060-006-9302-2

Titolo: Phase II study of imatinib mesylate and hydroxyurea for recurrent grade III malignant gliomas.

Autori: Desjardins A., Quinn JA., Vredenburgh JJ., Sathornsumetee S., Friedman AH., Herndon JE., McLendon RE., Provenzale JM., Rich JN., Sampson JH., Gururangan S., Dowell JM., Salvado A., Friedman HS., Reardon DA.

Data di Pubblicazione: 2007-1-25

Abstract: Imatinib mesylate plus hydroxyurea, is well tolerated and associated with anti-tumor activity in some patients with recurrent grade 3 MG.

Journal Title: Journal of neuro-oncology

PUBMED ID: 17228264

DOI: doi.org/10.1227/01.NEU.0000249203.73849.5D

Titolo: Genetic aberrations in gliomatosis cerebri.

Autori: Ware ML., Hirose Y., Scheithauer BW., Yeh RF., Mayo MC., Smith JS., Chang S., Cha S., Tihan T., Feuerstein BG.

Data di Pubblicazione: 2007-1-18

Abstract: Chromosomal aberrations associated with aggressive astrocytomas are predictors of poor outcome in patients with GC. This suggests that GC may be an architectural variant of diffuse astrocytomas. The presence of these aberrations and the presence of any contrast enhancement on magnetic resonance imaging scans are possible stratifiers for patients with GC. Stratification of GC into higher- and lower-grade forms may be useful in tailoring treatments to patients with this disease.

Journal Title: Neurosurgery

PUBMED ID: 17189147

DOI: doi.org/10.1016/j.jaapos.2006.03.014

Titolo: Orbital optic nerve gliomas in children with neurofibromatosis type 1.

Autori: Zeid JL., Charrow J., Sandu M., Goldman S., Listernick R.

Data di Pubblicazione: 2006-12-26

Abstract: Although not definitively proven, our data and previous studies suggest that NF-1-associated orbital optic nerve gliomas should not be treated unless there is clear evidence of either ophthalmologic or radiographic progression. Surgical excision of tumors which have led to proptotic eyes without functional vision should be reserved for cosmetic purposes or to treat complications of exposed globes.

Journal Title: Journal of AAPOS : the official publication of the American Association for Pediatric Ophthalmology and Strabismus

PUBMED ID: 17171442

DOI: doi.org/10.1007/s11060-006-9295-x

Titolo: Gliosarcoma with multiple extracranial metastases: case report and review of the literature.

Autori: Beaumont TL., Kupsky WJ., Barger GR., Sloan AE.

Data di Pubblicazione: 2006-12-16

Abstract: Gliosarcoma is a rare malignant neoplasm of the central nervous system with a propensity for metastasis. There are fewer than 20 reported cases of extracranial metastases of gliosarcoma with the majority of cases reflecting a tendency for hematogenous dissemination. Here we describe the case of a 47-year-old man who developed pervasive extracranial metastases from a temporal gliosarcoma following radio- and chemotherapy for a primary glioblastoma. The patient initially presented with progressively worsening headaches, left-sided weakness and numbness associated with right temporo-parietal mass for which he underwent craniotomy with stereotactic gross-total excision. Two months postoperatively, interstitial brachytherapy and external beam radiotherapy were initiated. The patient initially declined chemotherapy. The tumor recurred twice and the patient underwent re-operation and multiple courses of chemotherapy; histopathological diagnosis remained glioblastoma multiforme. Nineteen months following initial resection the patient's clinical status deteriorated and CT scan demonstrated multiple intrathoracic, hepatic and splenic lesions. Postmortem examination revealed widespread, infiltrating gliosarcoma with intravascular gliomatosis and extensive visceral metastases. This is the first report of pervasive extracranial metastases to numerous sites, several of which have not been previously reported. The histogenesis and the potential role of therapeutic irradiation in the development of gliosarcoma are briefly reviewed.

Journal Title: Journal of neuro-oncology

PUBMED ID: 17168505

DOI: doi.org/10.3171/foc.1998.4.4.8

Titolo: Low-grade gliomas in children: tumor volume response to radiation.

Autori: Fisher BJ., Bauman GS., Leighton CE., Stitt L., Cairncross JG., MacDonald DR.

Data di Pubblicazione: 2006-12-16

Abstract: Object. The authors conducted a retrospective review to examine and document the frequency, degree, and timing of the radiologically confirmed response to radiotherapy of low-grade gliomas in children. Methods. Between 1963 and 1995, 80 patients 17 years of age or younger were referred to the London Regional Cancer Centre in London, Ontario, after diagnosis of a low-grade glioma. All patients underwent surgical resection or biopsy procedures and 47 underwent radiotherapy (40 postoperatively and seven at the time of tumor progression). Nineteen patients with residual measurable lesions who rec



eived radiation therapy were selected for volumetric analysis of tumor response to this treatment. The extent and timing of response to radiation were determined by the process of comparing postoperative, preirradiation computerized tomography (CT) scans with postirradiation, follow-up CT scans. For one patient the comparison was made by using serial magnetic resonance images. Residual tumor was found on postoperative CT scans in all cases. The mean pre radiotherapy tumor volume was 17.1 cm(3), and the postradiotherapy volume was reduced to a mean of 11.5 cm(3). A reduction in tumor was demonstrated in eight patients by the time of their first postirradiation follow-up CT scan and in two patients a slower reduction in volume over time was shown, bringing the total number of "responders" to 10. In five of these 10 patients the tumor had shown a maximum response by the time of the first postirradiation CT scan; the median time to response was 3.3 months. A 25% or greater reduction in tumor volume was seen in eight (42%) of the 19 patients. A 50% or greater reduction was noted in five (26%) of the patients. A complete response was demonstrated at 7, 12, and 15 months, and 5 years, respectively, in four patients (21%). One responder's tumor eventually increased in size after radiotherapy and he died of his disease. The magnitude of the radiographically demonstrated response to radiation did not correlate significantly with clinical outcome (that is, survival or symptom improvement). Conclusions. On the basis of this CT scan analysis of the response of low-grade gliomas in children to radiotherapy, the authors suggest that these lesions respond to radiation, as demonstrated by tumor shrinkage on serial imaging. Major or complete responses occur occasionally. However, low-grade gliomas in children mimic other benign brain tumors such as pituitary adenomas and meningiomas in that, although growth is frequently arrested after radiotherapy, residual tumor can persist for many years, illustrating that tumor shrinkage may not be a good measure of treatment efficacy. Nevertheless, radiation therapy can result in improvement of clinical symptomatology in association with or independent of visible tumor reduction. As radiation treatment techniques become increasingly conformal and because studies indicate that lower doses of radiation may be equally effective, improvement of symptoms may be an important consideration when weighing treatment options, particularly in patients with residual or unresectable disease.

Journal Title: Neurosurgical focus

PUBMED ID: 17145324

DOI: doi.org/10.1016/j.surneu.2006.02.034

Titolo: Anaplastic oligodendroglioma responding favorably to intranasal delivery of perillyl alcohol: a case report and literature review.

Autori: Da Fonseca CO., Masini M., Futuro D., Caetano R., Gattass CR., Quirico-Santos T.

Data di Pubblicazione: 2006-12-6

Abstract: Whereas surgery continues to be the primary treatment for oligodendroglioma, the scheme for postoperative therapy has shifted primarily because of the lesion's relative chemosensitivity. This article evaluates the effects of intranasal delivery of POH in a case of regression of anaplastic oligodendroglioma.

Journal Title: Surgical neurology

PUBMED ID: 17102823

DOI: Mancante

Titolo: Medulloblastoma: conventional radiation therapy in comparison to chemoradiation therapy in the post-operative treatment of high-risk patients.

Autori: Abd El-Aal HH., Mokhtar MM., Habib E., El-Kashef AT., Fahmy ES.

Data di Pubblicazione: 2006-11-15

Abstract: The current treatment of medulloblastoma has a detrimental effect on long-term survivors. Whereas acute toxicity is considered mild and tolerable

ble, late toxicity regarding diminution in IQ makes current treatment unsatisfactory because of the long-term mental disability of the cured patients. We believe that, the poorer outcome in the chemo-radiation group was due to the treatment interruption during radiation therapy caused by myelosuppression since the incidence of myelosuppression was higher in the chemo-radiation group and the recovery time was longer.

Journal Title: Journal of the Egyptian National Cancer Institute

PUBMED ID: 17082887

DOI: doi.org/10.1007/s11060-006-9280-4

Titolo: Toxicity and efficacy of protracted low dose temozolomide for the treatment of low grade gliomas.

Autori: Pouratian N., Gasco J., Sherman JH., Shaffrey ME., Schiff D.

Data di Pubblicazione: 2006-11-4

Abstract: Protracted low dose temozolomide (75 mg/m<sup>2</sup>/day on days 1-21 of 28 days) offers potential advantages over standard temozolomide schedules (200 mg/m<sup>2</sup>/day on days 1-5 of 28 days) including greater cumulative drug exposure and depletion of O(6)-alkylguanine DNA alkyltransferase levels, theoretically overcoming intrinsic chemoresistance. We retrospectively review our experience in 25 patients with pathologically proven low grade gliomas (LGG) treated with protracted low dose temozolomide to primarily quantify its toxicity and secondarily to assess efficacy. None had previously received radiation. Tumor response was graded based on changes in tumor size, steroid requirements, and clinical exam. About 243 cycles of protracted low dose temozolomide were administered. Three patients (12%) were changed to standard temozolomide dosing due to side effects, including intractable nausea (n = 2) and multiple cytopenias (n = 1). The most frequent toxicities were fatigue (76%), lymphopenia (72% [48% high grade]), constipation (56%), and nausea (52%). High grade toxicities (other than lymphopenia) included secondary malignancy, pruritus, hyponatremia, neutropenia, leukopenia, and cognitive decline (n = 1 for each). Tumor response rate was 52% and disease control rate was 84%. Six month PFS was 92% and 12 month PFS was 72%. Response rates and PFS were independent of pathological subtype, deletion status, and indication for chemotherapy. Protracted low dose temozolomide has a distinct spectrum of toxicities compared to standard dosing but is well tolerated in most patients and may provide improved response rates compared to standard dosing. The results of larger randomized trials are needed to assess its potential advantages over other management schemes.

Journal Title: Journal of neuro-oncology

PUBMED ID: 17066462

DOI: doi.org/10.1002/pbc.21064

Titolo: High-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk or relapsed medulloblastoma or supratentorial primitive neuroectodermal tumor.

Autori: Sung KW., Yoo KH., Cho EJ., Koo HH., Lim DH., Shin HJ., Ahn SD., Ra YS., Choi ES., Ghim TT.

Data di Pubblicazione: 2006-10-27

Abstract: High-dose chemotherapy may improve the survival of children with newly diagnosed high-risk MB/sPNET, and, to some extent, the survival of those with relapsed MB/sPNET. Further study is necessary to elucidate the efficacy of tandem double HDCT.

Journal Title: Pediatric blood & cancer

PUBMED ID: 17053987

DOI: doi.org/10.1007/s10637-006-9017-4

Titolo: Phase I dose escalation clinical trial of phenylbutyrate sodium administered twice daily to patients with advanced solid tumors.

Autori: Camacho LH., Olson J., Tong WP., Young CW., Spriggs DR., Malkin MG.

Data di Pubblicazione: 2006-10-21

Abstract: Administration of PBA in a twice-daily infusion schedule is safe. The maximum tolerated dose is 300 mg/kg/day. Study designs with more convenient treatment schedules and specific molecular correlates may help to further delineate the mechanism of action of this compound. Future studies evaluating PBA's ability to induce histone acetylation and cell differentiation alone or in combination with other anti-neoplastics are recommended.

Journal Title: Investigational new drugs

PUBMED ID: 17047647

DOI: doi.org/10.1038/sj.bjc.6603402

Titolo: Secondary dissemination in children with high-grade malignant gliomas and diffuse intrinsic pontine gliomas.

Autori: Wagner S., Benesch M., Berthold F., Gnekow AK., Rutkowski S., Sträter R., Warmuth-Metz M., Kortmann RD., Pietsch T., Wolff JE.

Data di Pubblicazione: 2006-10-19

Abstract: In children, treatment regimen for high-grade gliomas (HGG) and diffuse intrinsic pontine gliomas (DIPG) are generally not stratified according to disease stage. The hypothesis was that secondary disseminating disease (SDD) in children with HGG is related to an even worse outcome. Description of SDD pattern was performed. In total, 270 children with newly diagnosed HGG or DIPG were eligible for retrospective analysis of SDD. Medical and computer records of these patients were reviewed for demographic characteristics, sites of dissemination, prognostic variables. Forty-six (17%) of the 270 patients had developed SDD. The median time to SDD was 8.2 months. The median overall survival (OS) after dissemination was 3.2 months. The SDD was located parenchymal in the supratentorial (34.8%), infratentorial (6.5%), supratentorial and infratentorial (19.6%), spinal (10.9%), spinal and cerebral (6.5%) regions of the CNS, or leptomeningeal (21.7%). For HGG patients, the median OS was shorter among patients with SDD than among patients without SDD (1.02 vs 1.41 years,  $P=0.0495$ ). In the group of patients with SDD, patients with cerebrospinal fluid dissemination had a worse outcome compared with patients with parenchymal metastases. Summarising, SDD is a negative prognostic factor for patients with HGG outside the pons. Treatment stratification should be considered.

Journal Title: British journal of cancer

PUBMED ID: 17032910

DOI: doi.org/10.1148/radiol.2413051276

Titolo: Malignant astrocytic tumors: clinical importance of apparent diffusion coefficient in prediction of grade and prognosis.

Autori: Higano S., Yun X., Kumabe T., Watanabe M., Mugikura S., Umetsu A., Sato A., Yamada T., Takahashi S.

Data di Pubblicazione: 2006-10-13

Abstract: The minimum ADC of malignant astrocytomas can provide additional information about their clinical malignancy related to posttreatment prognosis.

Journal Title: Radiology

PUBMED ID: 17031563

DOI: doi.org/10.1007/s11060-006-9219-9

Titolo: A case report and review of the literature.

Autori: Yomo S., Tada T., Hirayama S., Tachibana N., Otani M., Tanaka Y., Hongo K.

Data di Pubblicazione: 2006-10-13

Abstract: Primary diffuse leptomeningeal gliomatosis (PDLG) is a rare central nervous system neoplasm in which gliomatous tissue is diffusely identified in the subarachnoid space with no evidence of a primary intraparenchymal tumor. A 52-year-old man presented low back pain followed by sudden unconsciousness and had also cognitive dysfunction and meningeal signs. Examinations of cerebrospinal fluid (CSF) did not show malignant cells but increased protein and pleocytosis. Magnetic resonance (MR) imaging demonstrated diffuse leptomeningeal enhancement without any source of intraparenchymal lesion. Fluid-attenuated inversion recovery (FLAIR) also demonstrated individual diffuse high intensity areas in the subarachnoid space. A biopsy disclosed wide spreading of anaplastic glial cells within the leptomeninges. He died 3 months later because of disease progression despite both radiotherapy and chemotherapy. Post-mortem examination identified PDLG and several neuropathological features of glioblastoma as well. Reviewing previous cases of PDLG instructs that this entity is rare, resembles meningitis in clinical pictures, usually occurs in a relatively younger population and has more progressive clinical course than the ordinary form of malignant gliomas.

Journal Title: Journal of neuro-oncology

PUBMED ID: 16984371

DOI: doi.org/10.1111/j.1349-7006.2006.00272.x

Titolo: Personalized peptide vaccines: a new therapeutic modality for cancer .

Autori: Itoh K., Yamada A.

Data di Pubblicazione: 2006-9-21

Abstract: Therapeutic cancer vaccines have enjoyed little success so far, although many clinical trials have been conducted. Therefore, the creation of new protocols capable of inducing an objective response is required. We examined two of these protocols in the present review. The first is a personalized protocol to take into account the immunological diversity of cytotoxic T lymphocyte responses among patients. The second is a combination therapy designed to adapt to the presence of major histocompatibility complex (MHC)-loss cancer cells. The objective response rates of our classical (non-personalized) peptide vaccines were 0%, whereas that of personalized vaccines was 11.1% in the total advanced cancers and  $\geq 20\%$  in malignant glioma and cervical cancers, respectively. A  $\geq 50\%$  decrease in serum prostate-specific antigen (PSA) was seen in 8.7% of advanced hormone refractory prostate cancer patients by personalized vaccination alone, whereas such a decrease was seen in 54% of patients when the personalized vaccination was combined with a low dose of estramustine. Based on these experiences, we propose a personalized peptide vaccine combined with chemotherapy as a new treatment modality for cancers.

Journal Title: Cancer science

PUBMED ID: 16983574

DOI: doi.org/10.1007/s00381-006-0168-6

Titolo: Leptomeninges as a site of relapse in locally controlled, diffuse pontine glioma with review of literature.

Autori: Singh S., Bhutani R., Jalali R.

Data di Pubblicazione: 2006-9-20

Abstract: On follow-up, both patients showed clinical features suggestive of meningeal spread although imaging for pontine tumor showed stable disease. Leptomeningeal disease in the spine was confirmed on imaging and in one case by cerebrospinal fluid examination also. During the follow-up of patients with pontine glioma, the possibility of leptomeningeal involvement must be borne in mind.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 16944367

DOI: doi.org/10.1007/s10354-006-0308-3

Titolo: Molecular therapies for malignant glioma.

Autori: Hutterer M., Gunsilius E., Stockhammer G.

Data di Pubblicazione: 2006-9-1

Abstract: Due to the dismal prognosis of malignant glioma with currently available therapies there is an urgent need for new treatments based on a better molecular understanding of gliomagenesis. Several concepts of molecular therapies for malignant glioma are currently being studied in preclinical and clinical settings, including small molecules targeting specific receptor-mediated signaling pathways and gene therapy. Many growth factors, growth factor receptors--usually receptor tyrosine kinases--and receptor-associated signaling pathways are critically involved in gliomagenesis. Numerous selective inhibitors, which specifically block such molecules, are currently evaluated for clinical applicability. Several gene therapy approaches have shown antitumor efficacy in experimental studies, and the first clinical trials for the treatment of malignant glioma were conducted in the 1990s. In clinical trials, retroviral herpes-simplex-thymidinkinase- (HSV-Tk-) gene therapy has been the pioneering and most commonly used approach. However, efficient gene delivery into the tumor cells still remains the crucial obstacle for successful clinical gene therapy. During the past few years a number of new gene transfer vectors based on adeno-, adeno-associated-, herpes- and lentiviruses as well as new carrier cell systems, including neural and endothelial progenitor cells, have been developed. In addition, antisense technologies have advanced in recent years and entered clinical testing utilizing intratumoral administration by convection-enhanced delivery, exemplified by ongoing clinical trials of intratumoral administration of antisense TGF-beta. This paper summarizes some of these recent developments in molecular therapies for malignant glioma, focusing on targeted therapies using selective small molecules and gene therapy concepts.

Journal Title: Wiener medizinische Wochenschrift (1946)

PUBMED ID: 16944363

DOI: doi.org/10.1007/s10354-006-0304-7

Titolo: Malignant glioma: neuropathology and neurobiology.

Autori: Preusser M., Haberler C., Hainfellner JA.

Data di Pubblicazione: 2006-9-1

Abstract: Malignant gliomas may manifest at any age including congenital and childhood cases. Peak incidence is, however, in adults older than 40 years. Males are more frequently affected than females. The sole unequivocal risk factor is therapeutic ionizing irradiation. Malignant gliomas comprise a spectrum of different tumor subtypes. Within this spectrum, glioblastoma, anaplastic astrocytoma and anaplastic oligodendroglioma share as basic features preferential location in cerebral hemispheres, diffuse infiltration of brain tissue, fast tumor growth with fatal outcome within months or years. Invasion is regarded as one of the main reasons for poor therapeutic success, because it makes complete surgical removal of gliomas impossible. Invasion of glioma cells requires interaction with the extracellular matrix and with surrounding cells of the healthy brain tissue. Vascular proliferates and tissue necrosis are characteristic features of malignant gliomas, in particular glioblastoma. These features are most likely the consequence of rapidly increasing tumor mass that is inadequately oxygenized by the preexisting vasculature. In malignant glioma, distinct molecular pathways including the p53 pathway, the RB pathway and the EGFR pathway show frequent alterations that seem to be pathogenetically relevant. Methylguanine-methyltransferase (MGMT) promoter met

hylation status in glioblastoma and 1p19q deletion status in anaplastic oligodendroglioma are associated with response to chemotherapy. The role of neuropathology and neurobiology in neurooncology is 1. to provide a clinically meaningful classification of brain tumors on basis of pathobiological factors, 2. to clarify etiology and pathogenesis of brain tumors as rational basis for development of new diagnostic tests and therapies, and 3. to translate testing for new clinically relevant molecular parameters into clinical application.

Journal Title: Wiener medizinische Wochenschrift (1946)

PUBMED ID: 16914310

DOI: doi.org/10.1016/j.ejca.2006.05.021

Titolo: 1p/19q loss within oligodendroglioma is predictive for response to first line temozolomide but not to salvage treatment.

Autori: Kouwenhoven MC., Kros JM., French PJ., Biemond-ter Stege EM., Gravel and WJ., Taphoorn MJ., Brandes AA., van den Bent MJ.

Data di Pubblicazione: 2006-8-18

Abstract: Combined 1p/19q loss is mainly observed in classical OD. Responses to first line temozolomide are strongly correlated to loss of 1p. Response to second line alkylating treatment is modest even in tumours with 1p/19q loss. For further improvement of outcome in OD novel treatments are needed.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 16901454

DOI: doi.org/10.1177/08830738060210050901

Titolo: Second malignant neoplasms following the treatment of brain tumors in children.

Autori: Büyükpamukçu M., Varan A., Yazici N., Akalan N., Söylemezoğlu F., Zorlu F., Akyüz C., Kutluk MT.

Data di Pubblicazione: 2006-8-12

Abstract: We investigated retrospectively 992 children with central nervous system tumors who were treated at our center between 1970 and 2004. All of the patients were treated by surgery, chemotherapy, and/or radiotherapy. Six patients developed second malignant neoplasms, and their clinical and histopathologic characteristics are reviewed in this article. The second malignant neoplasms were diagnosed as non-Hodgkin lymphoma, myelodysplastic syndrome, basal cell carcinoma, malignant melanoma, Kaposi sarcoma, and high-grade neuroectodermal tumor. The initial diagnoses were ependymoblastoma in one, medulloblastoma in three, and low-grade astrocytoma in two patients. The median latency time was 3.03 years (range 0.39-22.93 years). The outcome varied according to the histopathologic type of the second tumor. The patients who developed non-Hodgkin lymphoma and myelodysplastic syndrome died of progressive disease. The patients with second skin neoplasms are alive as of the time of this writing. The patient with Kaposi sarcoma developed one of the rare reported second malignant neoplasms following a primary brain tumor in childhood. A wide spectrum of second malignant neoplasms was detected after treatment of primary brain tumors with surgery, radiotherapy, and chemotherapy. Long-term follow-up is therefore necessary for the child who has survived a primary central nervous system tumor.

Journal Title: Journal of child neurology

PUBMED ID: 16891823

DOI: doi.org/10.3346/jkms.2006.21.4.739

Titolo: Temozolomide chemotherapy in patients with recurrent malignant gliomas.

Autori: Yang SH., Kim MK., Lee TK., Lee KS., Jeun SS., Park CK., Kang JK., Kim MC., Hong YK.

Data di Pubblicazione: 2006-8-8

Abstract: Numerous studies have demonstrated the clinical activity of temozolomide, a second-generation alkylating agent, against malignant brain tumors, however, its activity has not been reported in an Asian population. This study analyzed the efficacy and toxicity of temozolomide in 25 adult patients with recurrent or progressive malignant gliomas after surgery and standard radiation therapy with or without chemotherapy, enrolled in our institution since July 2000. Sixteen patients had glioblastoma multiforme (GBM), six with anaplastic astrocytoma, and three with anaplastic oligodendroglioma. Of the 25 patients, 3 (12%) achieved a complete response (CR), 8 (32%) achieved a partial response (PR), 6 (24%) had stable disease (SD), and 8 (32%) had progressive disease (PD). Two patients achieved a CR, 4 patients achieved a PR, 3 patients had SD and 7 patients had PD in GBM, and 1 patient achieved a CR, 4 patients achieved a PR, 3 patients had SD, 1 patient had PD in the non-GBM patients. Median progression free survival was 8 weeks in GBM and 22 weeks in the non-GBM patients. The median overall survival of each group was 17 weeks and 28 weeks. Temozolomide demonstrated moderate activity in recurrent and progressive malignant gliomas without serious toxicity.

Journal Title: Journal of Korean medical science

PUBMED ID: 16873085

DOI: Mancante

Titolo: Primary and metastatic brain tumors.

Autori: Franceschi E., Scopece L., Gori S., Chiari R., Crino L.

Data di Pubblicazione: 2006-7-29

Abstract: High-grade malignant gliomas (HGG) are the most common and malignant primary central nervous system tumors. Despite therapeutic efforts and advances in biologic knowledge, these diseases remain lethal. Standard treatment of HGG is based on surgery and radiotherapy, usually followed by adjuvant chemotherapy. Many randomized trials addressing the role of post-radiation or "adjuvant" chemotherapy have been conducted in the last three decades, yielding inconclusive results. However, a statistically significant survival benefit with adjuvant chemotherapy has been demonstrated in two meta-analyses with nitrosourea-based adjuvant chemotherapy and a recent phase III trial has demonstrated a survival advantage for radiotherapy with concomitant and adjuvant temozolomide (TMZ) in patients with newly diagnosed glioblastoma. Since high-grade malignant gliomas can seldom be cured, the primary aim of treatments for recurrent disease is to improve progression-free survival (PFS), and to improve or preserve neurological functions. TMZ showed activity even in the treatment of recurrent HGG with a good toxicity profile, whether few data are available for effective treatments in patients treated with adjuvant TMZ. As a result, new agents and novel approaches are required. Furthermore, molecular studies to evaluate chemosensitivity predictors are necessary for patients' selection. Brain metastases are estimated to occur in 20% to 40% of cancer patients, with a higher risk in lung cancer, breast cancer and melanoma. The incidence of brain metastases is rising as results of better imaging procedures and improvements in treatments which leave more cancer patients at risk as survival increases. The prognosis is dependent on a number of factors such as histology of primary tumor, performance status, localization, number and size of brain metastases and status of extra cranial disease. Surgery and radiotherapy are indicated in controlled disease with isolated brain metastases. Systemic chemotherapy represents the optimal treatment in chemosensitive tumors with multiple or isolated brain metastases.

Journal Title: Forum (Genoa, Italy)

PUBMED ID: 16826191

DOI: doi.org/10.1038/sj.cgt.7700975

Titolo: Phase I clinical trial of a TGF-beta antisense-modified tumor cell vaccine in patients with advanced glioma.

Autori: Fakhrai H., Mantil JC., Liu L., Nicholson GL., Murphy-Satter CS., Ruppert J., Shawler DL.

Data di Pubblicazione: 2006-7-11

Abstract: We performed a phase I clinical trial in grade IV astrocytoma to assess the safety of a whole-cell vaccine comprising autologous tumor cells genetically modified by a transforming growth factor-beta2 (TGF-beta2) antisense vector. Blocking secretion of the immunosuppressive molecule TGF-beta in this manner should inhibit one of the major mechanisms by which tumor cells evade immune surveillance and should lead to clinically effective antitumor immunity. Six patients with progressive WHO grade IV astrocytoma were enrolled in the trial. Patients received 2-7 subcutaneous injections of  $5 \times 10^6$  -  $2 \times 10^7$  autologous tumor cells per injection. TGF-beta2 secretion by the tumor cells used to vaccinate patients was inhibited by 53-98%. Treatment was well tolerated with only low-grade, transient treatment-related toxicities reported. Two patients had partial regressions and two had stable disease following therapy. The overall median survival was 68 weeks. Median survival of the responding patients was 78 weeks, compared to a historic value of 47 weeks for glioma patients treated conventionally. There were indications of humoral and cellular immunity induced by the vaccine. These findings support further clinical evaluation of vaccines comprised of TGF-beta antisense-modified tumor cells.

Journal Title: Cancer gene therapy

PUBMED ID: 16817692

DOI: doi.org/10.3171/foc.2000.9.6.10

Titolo: Adoptive immunotherapy in patients with recurrent malignant glioma: preliminary results of using autologous whole-tumor vaccine plus granulocyte-macrophage colony-stimulating factor and adoptive transfer of anti-CD3-activated lymphocytes.

Autori: Sloan AE., Dansey R., Zamorano L., Barger G., Hamm C., Diaz F., Baynes R., Wood G.

Data di Pubblicazione: 2006-7-5

Abstract: These preliminary results suggest that autologous whole-tumor cell vaccines induce a cell-mediated immune response, which appears to be tumor specific in most patients. Furthermore, vaccination combined with adoptive immunotherapy with in vitro activated cells may induce a radiologically demonstrated tumor response and improved survival despite a condition of advanced disease and immunosuppression resulting from previous treatment or tumor burden. Further studies of immunotherapy are warranted.

Journal Title: Neurosurgical focus

PUBMED ID: 16816907

DOI: doi.org/10.1007/s10072-006-0609-8

Titolo: Transitory, spontaneously recovering, peripheral facial nerve palsy after vinorelbine administration.

Autori: Massimino M., Simonetti F., Balestrini MR., Spreafico F., La Spina M., Terenziani M., Gandola L.

Data di Pubblicazione: 2006-7-4

Abstract: Childhood intrinsic brain-stem gliomas have a dismal prognosis. Different treatment strategies have been adopted over the years without changing the final outcome of this ominous disease. Due to this grim prognosis, experimental therapeutic designs are worthwhile. Vinorelbine is a semi-synthetic vinca alkaloid that has demonstrated a broad spectrum of activity both in in vitro and in vivo experimental systems. By adopting vinorelbine during and after focal radiotherapy in the last two years, we have tried to evocate its known synergistic effect in brain-stem tumour control. Vinorelbine was ad



ministered intravenously before, during and after radiotherapy on tumour bed for a total duration of 10 months. All the consecutive patients whose clinical and radiological features corresponded to the diagnosis of an intrinsic brain-stem tumour, i.e., diffuse pontine glioma, have been accrued to this treatment protocol since July 2002. A histological assessment was not required. All patients were treated during hospital stay or in the outpatient clinic at the Istituto Nazionale Tumori of Milan (n=12) and at the Pediatric Clinic of Policlinico in Catania (n=1). Two of the thirteen patients so far treated have developed multiple subsequent, and transitory, episodes of monolateral peripheral facial nerve palsy during vinorelbine administration. The palsy always completely and spontaneously resolved at a short interval-around 30 min-after the end of the drug infusion. Obvious tumour progression was excluded by means of MRI; therefore the drug was administered as scheduled until the end of the treatment. We describe possible neurological and oncological implications of this unusual side effect, until now not reported in any other series dealing with vinorelbine as adjuvant treatment.

Journal Title: Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology

PUBMED ID: 16807782

DOI: doi.org/10.1007/s11060-006-9185-2

Titolo: Effectiveness of novel combination chemotherapy, consisting of 5-fluorouracil, vincristine, cyclophosphamide and etoposide, in the treatment of low-grade gliomas in children.

Autori: Lee MJ., Ra YS., Park JB., Goo HW., Ahn SD., Khang SK., Song JS., Kim YJ., Ghim TT.

Data di Pubblicazione: 2006-6-30

Abstract: Low-grade gliomas (LGG), which account for about 30% of brain tumors in children, are usually treated with surgical excision and/or radiotherapy. For patients who have significant residual tumor after resection or relapse after radiation, the proper chemotherapy regimen has not yet been identified. Thirteen children diagnosed with LGG outside the cerebellum between January 1999 and December 2004, all of whom had significant residual tumor after surgical resection, relapsed after radiation or showed visual deterioration, were treated for 18 months with a multi-drug regimen of vincristine, etoposide, cyclophosphamide and 5-fluorouracil. Of the 7 patients who completed chemotherapy, 1 showed complete response (CR), 5 showed partial response (PR), and 1 had stable disease (SD). In 5 patients, chemotherapy was prematurely discontinued; 4 of these patients showed tumor progression and 1 had SD. One patient is still undergoing treatment. The side effects of chemotherapy were manageable. The median time to tumor response was 34 months (range, 2-82 months). The progression free survival was 67.3%. Pediatric LGG patients with residual tumor after surgery or who undergo relapse(s) may be successfully treated using our combination chemotherapy regimen.

Journal Title: Journal of neuro-oncology

PUBMED ID: 16794761

DOI: doi.org/10.1007/s00508-006-0576-3

Titolo: Temozolomide for recurrent or progressive high-grade malignant glioma: results of an Austrian multicenter observational study.

Autori: Hassler M., Micksche M., Stockhammer G., Pichler J., Payer F., Abuja B., Deinsberger R., Marosi C.

Data di Pubblicazione: 2006-6-24

Abstract: The study data confirm the feasibility and efficacy of chemotherapy with temozolomide in patients with relapsed/progressive HGG.

Journal Title: Wiener klinische Wochenschrift

PUBMED ID: 16741299

DOI: Mancante

Titolo: Novel human IgG2b/murine chimeric antitenascin monoclonal antibody construct radiolabeled with <sup>131</sup>I and administered into the surgically created resection cavity of patients with malignant glioma: phase I trial results.

Autori: Reardon DA., Quinn JA., Akabani G., Coleman RE., Friedman AH., Friedman HS., Herndon JE., McLendon RE., Pegram CN., Provenzale JM., Dowell JM., Rich JN., Vredenburgh JJ., Desjardins A., Sampson JH., Gururangan S., Wong T Z., Badruddoja MA., Zhao XG., Bigner DD., Zalutsky MR.

Data di Pubblicazione: 2006-6-3

Abstract: The MTD of (<sup>131</sup>)I-ch81C6 is 2.96 GBq (80 mCi) because of dose-limiting hematologic toxicity. Although encouraging survival was observed, (<sup>131</sup>)I-ch81C6 was associated with greater hematologic toxicity, probably due to the enhanced stability of the IgG2 construct, than previously observed with (<sup>131</sup>)I-murine 81C6.

Journal Title: Journal of nuclear medicine : official publication, Society of Nuclear Medicine

PUBMED ID: 16645720

DOI: doi.org/10.1007/s11060-006-9144-y

Titolo: Carboplatin and etoposide (CE) chemotherapy in patients with recurrent or progressive oligodendroglial tumors.

Autori: Scopece L., Franceschi E., Cavallo G., Paioli A., Paioli G., Conforti R., Palmerini E., Berzioli C., Spagnolli F., Esposti RD., Crinò L.

Data di Pubblicazione: 2006-4-29

Abstract: In this trial CE regimen has shown relevant activity with a favorable safety profile.

Journal Title: Journal of neuro-oncology

PUBMED ID: 16645718

DOI: doi.org/10.1007/s11060-006-9147-8

Titolo: Maintenance treatment with interferon-gamma and low-dose cyclophosphamide for pediatric high-grade glioma.

Autori: Wolff JE., Wagner S., Reinert C., Gnekow A., Kortmann RD., Kühl J., Van Gool SW.

Data di Pubblicazione: 2006-4-29

Abstract: Maintenance treatment with IFN-gamma and low dose CPM has no sufficient beneficial effect for the treatment of high-grade glioma.

Journal Title: Journal of neuro-oncology

PUBMED ID: 16635428

DOI: doi.org/10.1007/s11910-006-0006-y

Titolo: Medulloblastoma: therapy and biologic considerations.

Autori: Gershon TR., Becher OJ.

Data di Pubblicazione: 2006-4-26

Abstract: Tremendous strides have been made in both the treatment and the biologic understanding of medulloblastoma. Present optimal treatment can cure most medulloblastoma patients. A substantial minority of patients, however, will have recurrent or progressive disease. Recent studies have demonstrated that the success of treatment is not simply a matter of chance, but rather can be predicted based on specific biologic markers. These markers predict outcome independent of clinical staging and make clear that medulloblastomas are a biologically diverse group of tumors with variable clinical behavior. Molecular biologic investigation, including replication of tumorigenesis in transgenic mice, has further elucidated the complex biology of medulloblastoma. Current standard and investigational treatments, however, do not yet make use of biologic markers that predict risk of recurrence. Practical limitations

ns have slowed the pace at which treatment paradigms can be revised to incorporate biologic insights. Mouse medulloblastoma models may provide an important bridge between biologic investigation and the development of new therapeutic approaches.

Journal Title: Current neurology and neuroscience reports

PUBMED ID: 16632619

DOI: doi.org/10.1259/bjr/30604050

Titolo: A four-dimensional computer simulation model of the in vivo response to radiotherapy of glioblastoma multiforme: studies on the effect of clonogenic cell density.

Autori: Stamatakos GS., Antipas VP., Uzunoglu NK., Dale RG.

Data di Pubblicazione: 2006-4-25

Abstract: Tumours behave as complex, self-organizing, opportunistic dynamic systems. In an attempt to better understand and describe the highly complicated tumour behaviour, a novel four-dimensional simulation model of in vivo tumour growth and response to radiotherapy has been developed. This paper presents the latest improvements to the model as well as a parametric validation of it. Improvements include an advanced algorithm leading to conformal tumour shrinkage, a quantitative consideration of the influence of oxygenation on radiosensitivity and a more realistic, imaging based description of the neovascularity distribution. The tumours selected for the validation of the model are a wild type and a mutated p53 gene glioblastomas multiforme. According to the model predictions, a whole tumour with larger cell cycle duration tends to repopulate more slowly. A lower oxygen enhancement ratio value leads to a more radiosensitive whole tumour. Higher clonogenic cell density (CCD) produces a higher number of proliferating tumour cells and, therefore, a more difficult tumour to treat. Simulation predictions agree at least semi-quantitatively with clinical experience, and particularly with the outcome of the Radiation Therapy Oncology Group (RTOG) Study 83-02. It is stressed that the model allows a quantitative study of the interrelationship between the competing influences in a complex, dynamic tumour environment. Therefore, the model can already be useful as an educational tool with which to study, understand and demonstrate the role of various parameters in tumour growth and response to irradiation. A long term quantitative clinical adaptation and validation of the model aiming at its integration into the treatment planning procedure is in progress.

Journal Title: The British journal of radiology

PUBMED ID: 16632439

DOI: doi.org/10.1007/s12094-006-0094-9

Titolo: Treatment of childhood diffuse brain stem tumors: comparison of results in different treatment modalities.

Autori: de Aquino Gorayeb MM., Aisen S., Nadalin W., Panico Gorayeb R., de Andrade Carvalho H.

Data di Pubblicazione: 2006-4-25

Abstract: Neither the association of radiation therapy with chemotherapy, tamoxifen nor both have showed survival improvement. The prognosis of these patients remains very poor and only investigational trials would justify a highly aggressive approach.

Journal Title: Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico

PUBMED ID: 16613322

DOI: doi.org/10.1016/j.humpath.2005.11.010

Titolo: Prognostic value of detecting recurrent glioblastoma multiforme in surgical specimens from patients after radiotherapy: should pathology evaluation alter treatment decisions?

Autori: Tihan T., Barletta J., Parney I., Lamborn K., Sneed PK., Chang S.

Data di Pubblicazione: 2006-4-15

Abstract: The prognostic significance of the histologic type and grade of gliomas at initial surgery is well established, but the value of histologic findings in resections after radiotherapy is unclear. Despite this uncertainty, pathologic interpretation of specimens after radiotherapy influences immediate treatment decisions. It is important to determine if, and to what extent, treatment decisions should be based on this information. We aimed to determine the prognostic value of pathologic evaluation in postradiation specimens from 54 patients with similar clinical features who underwent a second surgery for the treatment of radiologic worsening after external beam radiotherapy. We categorized the specimens from the second surgery as either recurrent tumor (category 1) or radionecrosis (category 2). Patients in category 1 had actively proliferating neoplasms with classical features of glioblastoma, whereas patients in category 2 had no evidence of tumor in their surgical specimens. Cases in which a clear-cut definition could not be made were labeled indeterminate (category 3). Despite the morphological evidence of tumor, there were no significant differences between categories 1 and 2 in any of the survival parameters tested. The only difference between groups was higher frequency of iodine 125 (125I) placement at second surgery in category 1 patients ( $P < .028$ ). Patients in category 1 with or without 125I treatment had similar survival characteristics. We conclude that histopathologic evaluation of postradiotherapy specimens was not helpful in predicting outcome or dictating further management. A comprehensive prospective study with advanced radiologic, pathologic, and molecular analyses may be more useful to determine prognostically valuable parameters.

Journal Title: Human pathology

PUBMED ID: 16598430

DOI: doi.org/10.1007/s11060-005-9087-8

Titolo: Extraneural metastatic medulloblastoma in an adult.

Autori: Wendland MM., Shrieve DC., Watson GA., Chin SS., Blumenthal DT.

Data di Pubblicazione: 2006-4-7

Abstract: Medulloblastoma is a rare malignancy in adults, accounting for approximately 1% of all primary brain tumors. Extraneural metastases have been reported in 10-30% of cases and most commonly involve bone; rarely lymph nodes, visceral organs and bone marrow may be involved with disease. We report here our experience with a 26 year-old woman with medulloblastoma treated with gross total resection followed by radiation therapy to her craniospinal axis. She subsequently developed widespread metastatic disease involving bone exclusive of the calvarium and spine for which multi-agent salvage chemotherapy was utilized with initial good clinical response. She later relapsed within the lymph nodes and soft tissues of the pelvis and eventually suffered a local recurrence within the posterior fossa. The treatment of medulloblastoma, particularly salvage therapy following disease recurrence, is reviewed.

Journal Title: Journal of neuro-oncology

PUBMED ID: 16598421

DOI: doi.org/10.1007/s11060-006-9125-1

Titolo: Disseminated pilocytic astrocytoma involving brain stem and diencephalon: a history of atypical eating disorder and diagnostic delay.

Autori: Distelmaier F., Janssen G., Mayatepek E., Schaper J., Göbel U., Rosenbaum T.

Data di Pubblicazione: 2006-4-7

**Abstract:** The association of weight loss and pediatric brain tumors that affect the diencephalon or brain stem with weight loss is a recognized, but not fully understood phenomenon. Tumors located in the hypothalamic region may induce the diencephalic syndrome (DS), which is characterized by profound emaciation with almost complete loss of subcutaneous fatty tissue. Tumors that compress or infiltrate the brain stem rarely cause both psychological disturbance and emaciation. The clinical presentation may be different, depending on the location of the lesion and age of the patient. In this report we present an unusual case of severe emaciation in a 4(9)/(12)-year-old girl with a juvenile pilocytic astrocytoma of the hypothalamic region and brain stem with neuroaxis dissemination. This case illustrates the importance of considering intracranial mass-lesions in the differential diagnosis of weight loss, psychological disturbance and atypical eating disorder. We discuss the importance of tumor multifocality and the role of patient age in the clinical presentation with reference to the literature.

**Journal Title:** Journal of neuro-oncology

**PUBMED ID:** 16533878

**DOI:** doi.org/10.1215/15228517-2005-010

**Titolo:** A phase 2 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American Brain Tumor Consortium study.

**Autori:** Prados MD., Lamborn K., Yung WK., Jaeckle K., Robins HI., Mehta M., Fine HA., Wen PY., Cloughesy T., Chang S., Nicholas MK., Schiff D., Greenberg H., Junck L., Fink K., Hess K., Kuhn J., Kuhn J.

**Data di Pubblicazione:** 2006-3-15

**Abstract:** The purpose of this study was to determine the response to CPT-11 administered every three weeks to adults with progressive malignant glioma, treated with or without enzyme-inducing antiepileptic drug (EIAED) therapy, at the recommended phase 2 dose determined from a previous phase 1 study. Adult patients age 18 or older with a KPS of 60 or higher who had measurable recurrent grade III anaplastic glioma (AG) or grade IV glioblastoma multiforme (GBM) were eligible. No more than one prior chemotherapy was allowed, either as adjuvant therapy or for recurrent disease. The CPT-11 dose was 350 mg/m<sup>2</sup> i.v. every three weeks in patients not on EIAED and 750 mg/m<sup>2</sup> in patients on EIAED therapy. Patients with stable or responding disease could be treated until tumor progression or a total of 12 months of therapy. The primary end point of the study was to determine whether CPT-11 could significantly delay tumor progression, using the rate of six-month progression-free survival (PFS-6). The trial was sized to be able to discriminate between a 15% and 35% rate for the GBM group alone and between a 20% and 40% rate for the entire cohort. There were 51 eligible patients, including 38 GBM and 13 AG patients, enrolled. The median age was 52 and 42 years, respectively. PFS-6 for the entire cohort was 17.6%. PFS-6 was 15.7% (95% confidence interval [CI], 0.07-0.31) for the GBM patients and 23% (95% CI, 0.07-0.52) for AG patients. Toxicity for the group included diarrhea and myelosuppression. We conclude that the recommended phase 2 dose of CPT-11 for patients with or without EIAED was ineffective on this schedule, in this patient population.

**Journal Title:** Neuro-oncology

**PUBMED ID:** 16525180

**DOI:** doi.org/10.1200/JCO.2005.04.5302

**Titolo:** Recent advances in the treatment of malignant astrocytoma.

**Autori:** Reardon DA., Rich JN., Friedman HS., Bigner DD.

**Data di Pubblicazione:** 2006-3-10

**Abstract:** Malignant gliomas, including the most common subtype, glioblastoma multiforme (GBM), are among the most devastating of neoplasms. Their aggressive infiltration in the CNS typically produces progressive and profound disability--ultimately leading to death in nearly all cases. Improvement in outc

ome has been elusive despite decades of intensive clinical and laboratory research. Surgery and radiotherapy, the traditional cornerstones of therapy, provide palliative benefit, while the value of chemotherapy has been marginal and controversial. Limited delivery and tumor heterogeneity are two fundamental factors that have critically hindered therapeutic progress. A novel chemoradiotherapy approach, consisting of temozolomide administered concurrently during radiotherapy followed by adjuvant systemic temozolomide, has recently demonstrated a meaningful, albeit modest, improvement in overall survival for newly diagnosed GBM patients. As cell-signaling alterations linked to the development and progression of gliomas are being increasingly elucidated, targeted therapies have rapidly entered preclinical and clinical evaluation. Responses to therapies that function via DNA damage have been associated with specific mediators of resistance that may also be subject to targeted therapies. Other approaches include novel locoregional delivery techniques to overcome barriers of delivery. The simultaneous development of multiple advanced therapies based on specific tumor biology may finally offer glioma patients improved survival.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 16524945

DOI: doi.org/10.1215/15228517-2005-009

Titolo: High-dose chemotherapy with stem cell rescue as initial therapy for anaplastic oligodendroglioma: long-term follow-up.

Autori: Abrey LE., Childs BH., Paleologos N., Kaminer L., Rosenfeld S., Salzman D., Finlay JL., Gardner S., Peterson K., Hu W., Swinnen L., Bayer R., Forsyth P., Stewart D., Smith AM., Macdonald DR., Weaver S., Ramsay DA., Nimer SD., DeAngelis LM., Cairncross JG.

Data di Pubblicazione: 2006-3-10

Abstract: We previously reported a phase 2 trial of 69 patients with newly diagnosed anaplastic or aggressive oligodendroglioma who were treated with intensive procarbazine, CCNU (lomustine), and vincristine (PCV) followed by high-dose thiotepa with autologous stem cell rescue. This report summarizes the long-term follow-up of the cohort of 39 patients who received high-dose thiotepa with autologous stem cell support. Thirty-nine patients with a median age of 43 (range, 18-67) and a median KPS of 100 (range, 70-100) were treated. Surviving patients now have a median follow-up of 80.5 months (range, 44-142). The median progression-free survival is 78 months, and median overall survival has not been reached. Eighteen patients (46%) have relapsed. Neither histology nor prior low-grade oligodendroglioma correlated with risk of relapse. Persistent nonenhancing tumor at transplant was identified in our initial report as a significant risk factor for relapse; however, long-term follow-up has not confirmed this finding. Long-term neurotoxicity has developed only in those patients whose disease relapsed and required additional therapy; no patient in continuous remission has developed a delayed neurologic injury. This treatment strategy affords long-term disease control to a subset of patients with newly diagnosed anaplastic oligodendroglioma without evidence of delayed neurotoxicity or myelodysplasia.

Journal Title: Neuro-oncology

PUBMED ID: 16523808

DOI: doi.org/10.1016/j.clon.2005.08.017

Titolo: Mathematical modelling of survival of glioblastoma patients suggests a role for radiotherapy dose escalation and predicts poorer outcome after delay to start treatment.

Autori: Burnet NG., Jena R., Jefferies SJ., Stenning SP., Kirkby NF.

Data di Pubblicazione: 2006-3-10

Abstract: Using the model, we have extracted biological information from clinical data. The model could be used to assess the potential benefit, or lack of benefit, from a proposed radiotherapy trial, and to estimate the necessary size. It shows that a single modality is unlikely to achieve a major improvement in long-term survival, although radiotherapy dose escalation should have a role, provided it can be given safely. The model could be extended to include chemotherapy, bio-reductive drugs, or gene therapy.

Journal Title: Clinical oncology (Royal College of Radiologists (Great Britain))

PUBMED ID: 16510333

DOI: doi.org/10.1016/S1470-2045(06)70615-5

Titolo: Diffuse brainstem glioma in children: critical review of clinical trials.

Autori: Hargrave D., Bartels U., Bouffet E.

Data di Pubblicazione: 2006-3-3

Abstract: Diffuse intrinsic brainstem gliomas constitute 15-20% of all CNS tumours in children, and are the main cause of death in children with brain tumours. Many clinical trials have been done over the past three decades, but survival has remained static. More than 90% of children die within 2 years of diagnosis, and conventional fractionated radiation remains the standard treatment. However, median survival differs substantially between clinical trials, suggesting a survival benefit with some strategies. We appraised the consistency between protocols in terms of eligibility criteria, definition and assessment of response and progression, statistical design, and endpoints. Study designs varied substantially, which could explain the differences in outcome, and no treatment has shown a benefit over conventional radiotherapy. However, consistency between protocols (eg, eligibility criteria and outcome measures) is important to measure the progress in management of diffuse pontine gliomas.

Journal Title: The Lancet. Oncology

PUBMED ID: 16484713

DOI: doi.org/10.1177/1534735405285380

Titolo: Targeted therapy with antineoplastons A10 and AS2-1 of high-grade, recurrent, and progressive brainstem glioma.

Autori: Burzynski SR., Janicki TJ., Weaver RA., Burzynski B.

Data di Pubblicazione: 2006-2-18

Abstract: Antineoplastons contributed to more than a 5-year survival in recurrent diffuse intrinsic glioblastomas and anaplastic astrocytomas of the brainstem in a small group of patients.

Journal Title: Integrative cancer therapies

PUBMED ID: 16467100

DOI: doi.org/10.1158/1078-0432.CCR-05-2215

Titolo: Phase 1 trial of gefitinib plus sirolimus in adults with recurrent malignant glioma.

Autori: Reardon DA., Quinn JA., Vredenburgh JJ., Gururangan S., Friedman AH., Desjardins A., Sathornsumetee S., Herndon JE., Dowell JM., McLendon RE., Pirovanzale JM., Sampson JH., Smith RP., Swaisland AJ., Ochs JS., Lyons P., Tortorici S., Bigner DD., Friedman HS., Rich JN.

Data di Pubblicazione: 2006-2-10

Abstract: We show that gefitinib plus sirolimus can be safely coadministered on a continuous, daily dosing schedule, and established the recommended dose level of these agents in combination for future phase 2 clinical trials.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 16463390

DOI: doi.org/10.1002/cncr.21749

Titolo: Intratumoral hemorrhage among children with newly diagnosed, diffuse brainstem glioma.

Autori: Broniscer A., Laningham FH., Kocak M., Krasin MJ., Fouladi M., Merchant TE., Kun LE., Boyett JM., Gajjar A.

Data di Pubblicazione: 2006-2-8

Abstract: Although IH is uncommon at the time of diagnosis, symptomatic IH may occur among nearly 20% of children after the diagnosis of BSG. The uniform occurrence of IH among patients treated with various chemotherapeutic regimens and its association with necrotic areas suggests that tumor biology plays a significant role in this event.

Journal Title: Cancer

PUBMED ID: 16448552

DOI: doi.org/10.1186/1471-2407-6-29

Titolo: A phase 1-2, prospective, double blind, randomized study of the safety and efficacy of Sulfasalazine for the treatment of progressing malignant gliomas: study protocol of [ISRCTN45828668].

Autori: Robe PA., Martin D., Albert A., Deprez M., Chariot A., Bours V.

Data di Pubblicazione: 2006-2-2

Abstract: The aim of this study is to evaluate the safety and efficacy of Sulfasalazine as a treatment for recurring malignant gliomas. The safety and efficacy of this drug are analyzed as primary endpoints. Overall survival and progression-free survival are secondary endpoint.

Journal Title: BMC cancer

PUBMED ID: 16443950

DOI: doi.org/10.1215/S1522851705000451

Titolo: Phase 1 study of erlotinib HCl alone and combined with temozolomide in patients with stable or recurrent malignant glioma.

Autori: Prados MD., Lamborn KR., Chang S., Burton E., Butowski N., Malec M., Kapadia A., Rabbitt J., Page MS., Fedoroff A., Xie D., Kelley SK.

Data di Pubblicazione: 2006-1-31

Abstract: The purpose of this study was to define the maximum tolerated dose of erlotinib and characterize its pharmacokinetics and safety profile, alone and with temozolomide, with and without enzyme-inducing antiepileptic drugs (EIAEDs), in patients with malignant gliomas. Patients with stable or progressive malignant primary glioma received erlotinib alone or combined with temozolomide in this dose-escalation study. In each treatment group, patients were stratified by coadministration of EIAEDs. Erlotinib was started at 100 mg orally once daily as a 28-day treatment cycle, with dose escalation by 50 mg/day up to 500 mg/day. Temozolomide was administered at 150 mg/m<sup>2</sup> for five consecutive days every 28 days, with dose escalation up to 200 mg/m<sup>2</sup> at the second cycle. Eightythree patients were evaluated. Rash, fatigue, and diarrhea were the most common adverse events and were generally mild to moderate. The recommended phase 2 dose of erlotinib is 200 mg/day for patients with glioblastoma multiforme who are not receiving an EIAED, 450 mg/day for those receiving temozolomide plus erlotinib with an EIAED, and at least 500 mg/day for those receiving erlotinib alone with an EIAED. Of the 57 patients evaluable for response, eight had a partial response (PR). Six of the 57 patients had a progression-free survival of longer than six months, including four patients with a PR. Coadministration of EIAEDs reduced exposure to erlotinib as compared with administration of erlotinib alone (33%-71% reduction). There was a modest pharmacokinetic interaction between erlotinib and temozolomide.



The favorable tolerability profile and evidence of antitumor activity indicate that further investigation of erlotinib is warranted.  
Journal Title: Neuro-oncology

PUBMED ID: 16435380  
DOI: doi.org/10.1002/pbc.20739  
Titolo: Topotecan by 21-day continuous infusion in children with relapsed or refractory solid tumors: a Children's Oncology Group study.  
Autori: Hawkins DS., Bradfield S., Whitlock JA., Krailo M., Franklin J., Blaney SM., Adamson PC., Reaman G.  
Data di Pubblicazione: 2006-1-26  
Abstract: Intravenous topotecan by 21-day continuous infusion is tolerable in pediatric patients with recurrent or refractory solid tumors. Limited activity was seen in ESFT and further development of this topotecan schedule as a single agent is not warranted.  
Journal Title: Pediatric blood & cancer

PUBMED ID: 16391896  
DOI: doi.org/10.1007/s11060-005-9062-4  
Titolo: Combination chemotherapy with 13-cis-retinoic acid and celecoxib in the treatment of glioblastoma multiforme.  
Autori: Levin VA., Giglio P., Puduvalli VK., Johech J., Groves MD., Yung WK., Hess K.  
Data di Pubblicazione: 2006-1-5  
Abstract: In a phase II clinical trial, we sought to determine if combining celecoxib with 13-cis-retinoic acid (13-cRA, Accutane) was efficacious in the treatment of recurrent (progressive) glioblastoma multiforme (GBM). In parallel, we also sought to determine to what extent the outcomes from this clinical trial correlated with the findings from studies utilizing two murine intracerebral GBM models, U87MG and U251HF, to determine the predictive value of these murine models. In the clinical trial, 25 patients were studied at recurrence. Stable disease, which occurred in 44% of the patients, was the best response. The median progression-free survival (PFS) was 8 weeks, with a PFS at 6 months of only 19%. For the patients with stable disease, the median PFS was 24 weeks. The toxicity profile was unremarkable. The modest effect on PFS seen in this study agreed with the recent findings of another study, which showed a 19% PFS at 6 months in patients treated with 13-cRA alone. Thus, the combination of 13-cRA with celecoxib is not more effective than 13-cRA in the treatment of progressive GBM. In the murine model study, we found that long-term dosing with 13-cRA or celecoxib alone or in combination did not increase survival in animals with U87MG tumors but modestly increased survival in animals with U251HF tumors. There was no evidence of synergism between the two drugs. From this, we concluded that the animal studies generally predicted that the two agents would have only a modest effect alone and no additive effect when given in combination to patients.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 16378678  
DOI: doi.org/10.1016/j.clineuro.2005.11.015  
Titolo: Anaplastic oligodendroglioma and gliomatosis type 2 in interferon-beta treated multiple sclerosis patients. Report of two cases.  
Autori: Segal S., Horvat A., Popovic M.  
Data di Pubblicazione: 2005-12-28  
Abstract: The concurrence of multiple sclerosis (MS) and brain tumors has been reported, but it is not known whether MS patients are at greater risk of harbouring the latter. The most common cerebral neoplasms reported in MS patients were oligodendroglioma, astrocytoma, glioblastoma and gliomatosis. MS

can also present as a mass lesion that mimics a brain tumor. To establish the correct diagnosis radiological follow-up and/or histological confirmation is needed. Two cases of coincidental MS and brain tumors are reviewed. One is a 26-year-old woman with relapsing-remitting MS and an anaplastic oligodendroglioma, the other a 49-year-old woman patient with relapsing-remitting MS and gliomatosis type 2. Both patients were treated with interferon-beta and both died from the tumor. The concurrence of MS and brain tumors could be purely coincidental, or the result of neoplastic transformation of reactive glial cells in the areas of demyelination. The combination of a brain tumor and MS, and interferon-beta treatment could also be pure coincidence or an unknown side effect of treatment. Although interferon-beta has been said to function as a tumor-suppressor protein, the influence of long-term treatment of MS patients on cancer development is not known.

Journal Title: Clinical neurology and neurosurgery

PUBMED ID: 16374565

DOI: doi.org/10.1007/s00701-005-0694-0

Titolo: Role of temozolomide in spinal cord low grade astrocytomas: results in two paediatric patients.

Autori: Chamoun RB., Alaraj AM., Al Kutoubi AO., Abboud MR., Haddad GF.

Data di Pubblicazione: 2005-12-24

Abstract: Based on our findings in two paediatric patients, temozolomide may be a useful agent in the management of progressive recurrent low grade spinal cord astrocytomas.

Journal Title: Acta neurochirurgica

PUBMED ID: 16361636

DOI: doi.org/10.1200/JCO.2005.03.2185

Titolo: Phase II study of imatinib mesylate plus hydroxyurea in adults with recurrent glioblastoma multiforme.

Autori: Reardon DA., Egorin MJ., Quinn JA., Rich JN., Rich JN., Gururangan S., Gururangan I., Vredenburgh JJ., Desjardins A., Sathornsumetee S., Provenzale JM., Herndon JE., Dowell JM., Badrudoja MA., McLendon RE., Lagattuta TF., Kiczielinski KP., Dresemann G., Sampson JH., Friedman AH., Salvado AJ., Friedman HS.

Data di Pubblicazione: 2005-12-20

Abstract: Imatinib mesylate plus hydroxyurea is well tolerated and associated with durable antitumor activity in some patients with recurrent GBM.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 16334150

DOI: Mancante

Titolo: Treatment of unresectable glioblastoma multiforme.

Autori: Nieder C., Grosu AL., Astner S., Molls M.

Data di Pubblicazione: 2005-12-13

Abstract: Uncertainty exists about the adequate treatment of adult patients with unresectable, primary, biopsy-proven glioblastoma multiforme (GBM), because the different options for this group of patients have not been evaluated in randomized clinical trials to date. Usually, these patients are lumped together in studies of radiotherapy or combined modality treatment with patients who have undergone extensive surgical resection, although they represent an unfavorable subgroup. This fact led us to review the recently published results for combined radio- and chemotherapy and to compare them with historical data. Management with best supportive care after biopsy resulted in a median survival time of 3 months. Median survival in a historical series of radiotherapy was of the order of 6-7 months and 2-year survival was less than

10%. Combined treatment consistently resulted in a 2-year survival rate of 10-18%. However, the median survival in contemporary series is highly variable, still ranging from 5 to 13 months. Even with the same regimen, large differences in outcome were observed (median survival 5 vs. 9.4 months). In a large randomized trial of radiotherapy vs. radiotherapy plus temozolomide, the subgroup with biopsy only did not benefit significantly from combined treatment. With different radiochemotherapy approaches, the median survival was approximately 5 months in recursive partitioning analysis (RPA) class VI, but 8-14 months in classes IV and V. Thus, careful patient selection is necessary to avoid overtreatment in prognostically unfavorable groups with unresectable GBM. In patients qualifying for lengthy regimens of radio-chemotherapy, prospective randomized trials should study whether simultaneous radio- and chemotherapy is superior to radiotherapy alone and, if so, what are the effects of addition of either upfront chemotherapy or post-radiation chemotherapy. Recent data suggest that class prediction models, based on defined molecular profiles, and assessment of MGMT promoter methylation might contribute to improved patient stratification and decision making.

Journal Title: Anticancer research

PUBMED ID: 16323194

DOI: doi.org/10.1002/cncr.21582

Titolo: Salvage chemotherapy with cyclophosphamide for recurrent temozolomide-refractory anaplastic astrocytoma.

Autori: Chamberlain MC., Tsao-Wei DD., Groshen S.

Data di Pubblicazione: 2005-12-3

Abstract: CYC demonstrated modest efficacy with acceptable toxicity in this cohort of adult patients with recurrent anaplastic astrocytoma, all of whom had failed prior TMZ chemotherapy.

Journal Title: Cancer

PUBMED ID: 16315242

DOI: doi.org/10.1002/cncr.21593

Titolo: Phase II study of high-dose chemotherapy before radiation in children with newly diagnosed high-grade astrocytoma: final analysis of Children's Cancer Group Study 9933.

Autori: MacDonald TJ., Arenson EB., Ater J., Spoto R., Bevan HE., Bruner J., Deutsch M., Kurczynski E., Luerksen T., McGuire-Cullen P., O'Brien R., Shah N., Steinbok P., Strain J., Thomson J., Holmes E., Vezina G., Yates A., Phillips P., Packer R.

Data di Pubblicazione: 2005-11-30

Abstract: OS and EFS were not affected by histologic grade. Patients who responded to HDCT had a nominally higher survival rate ( $P = 0.03$  for trend). The authors conclude that these commonly used HDCT regimens provide no additional clinical benefit to conventional treatment in HGA, regardless of the amount of measurable residual tumor.

Journal Title: Cancer

PUBMED ID: 16300848

DOI: doi.org/10.1016/j.radonc.2005.10.016

Titolo: Role of radiotherapy in anaplastic ependymoma in children under age of 3 years: results of the prospective German brain tumor trials HIT-SKK 87 and 92.

Autori: Timmermann B., Kortmann RD., Kühl J., Rutkowski S., Dieckmann K., Meisner C., Bamberg M.

Data di Pubblicazione: 2005-11-23

Abstract: Delaying RT jeopardizes survival even after intensive chemotherapy . Predominant site of failure is the primary tumor site. RT of the neuraxis should be omitted in localized disease.

Journal Title: Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology

PUBMED ID: 16283445

DOI: doi.org/10.1007/s11060-005-3030-x

Titolo: Systemic temozolomide combined with loco-regional mitoxantrone in treating recurrent glioblastoma.

Autori: Boiardi A., Eoli M., Salmaggi A., Lamperti E., Botturi A., Broggi G., Bissola L., Finocchiaro G., Silvani A.

Data di Pubblicazione: 2005-11-12

Abstract: Twenty-two recurrent GBM patients were enrolled for second tumor debulking with local positioning of a Rickam reservoir, in order to locally deliver chemotherapy with the aim of controlling local tumor recurrence. We designed a protocol using systemic temozolomide (150 mg/sqm days 1-5 every 28) in association with mitoxantrone, delivered through the reservoir (4 mg/day 1-5 every 28) positioned into the area of tumor exeresis. After re-operation a residual tumor mass no larger than 2 cm was identified in 18/22 patients. The patients were treated with monthly cycles of chemotherapy until evolution of the tumor, but in no case for more than 10 cycles. Responses were evaluated by MRI scans performed every 2 months and images assessed according to MacDonald's criteria. Response rate: no complete responses (CR), 5 partial responses (PR), 13 stable disease (SD) and 4 progressive disease (PD) occurred. The median progression-free survival (PFS) and survival time (ST) of the whole group of treated patients was 7 and 11 months, respectively and more than a quarter of the patients survived over 18 months. During the study, the patients' compliance was complete and no dropouts occurred. Hematological toxicity was mild and after repeated local injections only minor neurological side-effects occurred. Despite some bias in patients' selection not excluded in this pilot study, results are interesting: the PFS was as long as the survival of recurrent GBM reported in the literature.

Journal Title: Journal of neuro-oncology

PUBMED ID: 16267128

DOI: doi.org/10.1073/pnas.0508347102

Titolo: Evaluation of the functional diffusion map as an early biomarker of time-to-progression and overall survival in high-grade glioma.

Autori: Hamstra DA., Chenevert TL., Moffat BA., Johnson TD., Meyer CR., Mukherji SK., Quint DJ., Gebarski SS., Fan X., Tsien CI., Lawrence TS., Junck L., Rehemtulla A., Ross BD.

Data di Pubblicazione: 2005-11-4

Abstract: Diffuse malignant gliomas, the most common type of brain tumor, carry a dire prognosis and are poorly responsive to initial treatment. The response to treatment is typically evaluated by measurements obtained from radiographic images several months after the start of treatment; therefore, an early biomarker of tumor response would be useful for making early treatment decisions and for prognostic information. Thirty-four patients with malignant glioma were examined by diffusion MRI before treatment and 3 weeks later. These images were coregistered, and differences in tumor-water diffusion values were calculated as functional diffusion maps (fDM), which were correlated with the radiographic response, time-to-progression (TTP), and overall survival (OS). Changes in fDM at 3 weeks were closely associated with the radiographic response at 10 weeks. The percentage of the tumor undergoing a significant change in the diffusion of water (V(T)) was different between patients with progressive disease (PD) vs. stable disease (SD) ( $P < 0.001$ ). Patients classified as PD by fDM analysis at 3 weeks were found to have a shorter T

TP compared with SD (median TTP, 4.3 vs. 7.3 months;  $P < 0.04$ ). By using fDM, early patient stratification also was correlated with shorter OS in the PD group compared with SD patients (median survival, 8.0 vs. 18.2 months;  $P < 0.01$ ). On the basis of fDM, tumor assessment provided an early biomarker for response, TTP, and OS in patients with malignant glioma. Further evaluation of this technique is warranted to determine whether it may be useful in the individualization of treatment or evaluation of the response in clinical protocols.

Journal Title: Proceedings of the National Academy of Sciences of the United States of America

PUBMED ID: 16265674

DOI: doi.org/10.1002/cncr.21534

Titolo: Topotecan as a radiosensitizer in the treatment of children with malignant diffuse brainstem gliomas: results of a French Society of Paediatric Oncology Phase II Study.

Autori: Bernier-Chastagner V., Grill J., Doz F., Bracard S., Gentet JC., Marie-Cardine A., Luporsi E., Margueritte G., Lejars O., Laithier V., Mechinaud F., Millot F., Kalifa C., Chastagner P.

Data di Pubblicazione: 2005-11-3

Abstract: The findings of the current study regarding newly diagnosed brainstem glioma patients treated with topotecan given as a radiosensitizing agent did not reproduce the encouraging results obtained in preclinical studies. Therefore, the concomitant combination of topotecan and radiotherapy at this schedule and these doses cannot be recommended for the treatment of patients with brainstem gliomas.

Journal Title: Cancer

PUBMED ID: 16241105

DOI: doi.org/10.3171/foc.2005.19.4.4

Titolo: Emerging concepts in glioma biology: implications for clinical protocols and rational treatment strategies.

Autori: Wiesner SM., Freese A., Ohlfest JR.

Data di Pubblicazione: 2005-10-26

Abstract: Glioblastoma multiforme (GBM), the most common primary central nervous system neoplasm, is a complex, heterogeneous disease. The recent identification of stem cells in murine tumor xenografts that were capable of recapitulating the tumor phenotype adds a new dimension of complexity to the already challenging treatment of patients with GBMs. Although specific cellular and genetic changes are commonly associated with GBM, the mechanism by which those changes occur may have a significant impact on treatment outcome. Of the many bioinformatics techniques developed in recent years, gene expression profiling has become a commonly used research tool for investigating tumor characteristics, and the development of rationally targeted molecular therapies has also accelerated following the initial success of specifically designed inhibitors in the treatment of malignancies. Despite these advances in research techniques and targeted molecular therapies, however, limited clinical impact has been achieved in the treatment of infiltrative malignancies such as GBMs. Thus, further extension in survival of patients with GBMs may require use of multiple analyses of tumors to develop tailored therapies that reflect the inter- and intratumoral heterogeneity of this disease. In this review, the authors briefly consider the potential use of expression profiling combined with mutation analysis in the development of treatment modalities to address the heterogeneity of this complex tumor phenotype.

Journal Title: Neurosurgical focus

PUBMED ID: 16234523

DOI: doi.org/10.1200/JCO.2005.09.095

Titolo: Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group.

Autori: Geyer JR., Sposto R., Jennings M., Boyett JM., Axtell RA., Breiger D., Broxson E., Donahue B., Finlay JL., Goldwein JW., Heier LA., Johnson D., Mazewski C., Miller DC., Packer R., Puccetti D., Radcliffe J., Tao ML., Shiminski-Maher T., Shiminski-Maher T.

Data di Pubblicazione: 2005-10-20

Abstract: Intensified induction chemotherapy resulted in a high response rate of malignant brain tumors in infants. Survival was comparable to that of previous studies, and most patients who survived did not receive radiation therapy.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 16206736

DOI: doi.org/10.3171/ped.2005.102.1.0065

Titolo: Spontaneous regression of a diffuse brainstem lesion in the neonate. Report of two cases and review of the literature.

Autori: Thompson WD., Kosnik EJ.

Data di Pubblicazione: 2005-10-7

Abstract: The authors present two cases of diffuse brainstem lesions that regressed without treatment. Two newborns presented with cranial nerve palsies and limb weakness at birth. Magnetic resonance (MR) images obtained in the 1st week of life revealed a large, expansive pontomedullary lesion in each patient. Findings of clinical and imaging examinations were highly consistent with the characteristics of diffuse brainstem glioma. After consultation with the parents of both infants, all parties agreed to forgo the treatment modalities available at the time. Neither patient underwent surgery, radiation treatment, or chemotherapy; both underwent routine neurological and MR imaging examinations. Within weeks the patient in Case 1 started to improve clinically and at 4 years of age has reached nearly all developmental milestones. Serial MR images demonstrated a steady decrease in the size of the lesion. The patient in Case 2 improved in a similar manner and is now 10 years old. The findings from these two cases should encourage families and clinicians to consider that a subcategory of diffuse lesions may exist, particularly in the neonatal period. It must be stressed, however, that nearly all patients with diffuse brainstem lesions experience a poor outcome, regardless of tumor grade or treatment. Brainstem gliomas, spontaneous regression of central nervous system tumors, and the differential diagnoses of brainstem lesions are discussed.

Journal Title: Journal of neurosurgery

PUBMED ID: 16184181

DOI: doi.org/10.1038/sj.bmt.1705162

Titolo: High-dose busulfan and thiotepa followed by autologous stem cell transplantation (ASCT) in previously irradiated medulloblastoma patients: high toxicity and lack of efficacy.

Autori: Valteau-Couanet D., Fillipini B., Benhamou E., Grill J., Kalifa C., Couanet D., Habrand JL., Hartmann O.

Data di Pubblicazione: 2005-9-27

Abstract: We previously demonstrated that Busulfan-Thiotepa (Bu-Thio) and ASCT effectively treated patients with locally relapsed medulloblastoma after surgery and conventional chemotherapy. We thus evaluated the administration of Bu-Thio in patients relapsing after conventional CNS irradiation. Patients were scheduled to receive Busulfan (600 mg/m<sup>2</sup>) and Thiotepa (900 mg/m<sup>2</sup>) and ASCT. Resection of residual tumour and additional irradiation were performed if necessary and feasible after Bu-Thio. Toxicity was compared to tha

t observed in 35 patients treated without previous CNS irradiation. From 5/88 to 3/02, 15 patients were treated according to this strategy. Toxicity was significantly higher than that observed in unirradiated patients: thrombocytopenia  $<50,000/\text{mm}^3$  lasting 56 days (13-732) ( $P=0.02$ ) and 30 days (4-124), respectively, HVD (10/15 and 12/35 patients, respectively) ( $P=0.06$ ), neurological toxicity (8/15 vs 3/35 patients) ( $P=0.01$ ). Tumour response was assessable in seven patients and consisted in two CR, three PR and two NR. Currently, two of 15 patients are alive with no evidence of disease. In conclusion, the toxicity of Bu-Thio was significantly more severe in previously irradiated patients. In spite of a high response rate, this strategy failed to improve the prognosis of previously irradiated patients with a relapse from a medulloblastoma.

Journal Title: Bone marrow transplantation

PUBMED ID: 16177987

DOI: doi.org/10.1002/cncr.21403

Titolo: A Phase I study of concurrent RMP-7 and carboplatin with radiation therapy for children with newly diagnosed brainstem gliomas.

Autori: Packer RJ., Krailo M., Mehta M., Warren K., Allen J., Jakacki R., Villablanca JG., Chiba A., Reaman G.

Data di Pubblicazione: 2005-9-24

Abstract: The results of this study confirmed the feasibility of giving RMP-7 and carboplatin daily during radiotherapy to children with brainstem tumors.

Journal Title: Cancer

PUBMED ID: 16156235

DOI: doi.org/10.3171/jns.2005.102.2.0224

Titolo: Atypical external hydrocephalus with visual failure due to occult leptomeningeal dissemination of a pontine glioma. Case report.

Autori: Tarnaris A., Edwards RJ., Lewis SP., Pople IK.

Data di Pubblicazione: 2005-9-15

Abstract: The authors report on the case of a diffuse pontine glioma in a 5-year-old boy in whom radiologically and cytologically occult leptomeningeal metastases led to the development of an atypical "external" hydrocephalus, associated with grossly elevated intracranial pressure (ICP). Initial neuroimaging demonstrated only mild communicating ventricular dilation associated with a noticeable enlargement of the subarachnoid space, particularly over the surface of the frontal lobes; these features are not usually associated with significantly elevated ICP. Possible pathophysiological mechanisms resulting in this unusual clinical presentation are discussed. Early recognition of the severity of the raised ICP despite the paucity of clinical and radiological signs may have averted the development of blindness due to optic atrophy.

Journal Title: Journal of neurosurgery

PUBMED ID: 16151595

DOI: doi.org/10.1007/s11060-005-5261-2

Titolo: Multisection 1H magnetic resonance spectroscopic imaging assessment of glioma response to chemotherapy.

Autori: Balmaceda C., Critchell D., Mao X., Cheung K., Pannullo S., DeLaPaz RL., Shungu DC.

Data di Pubblicazione: 2005-9-10

Abstract: This study evaluated the role of proton magnetic resonance spectroscopic imaging (1H MRSI) in assessing the response of low-grade brain tumors to a chemotherapy-only treatment regimen. Specifically, it was of interest to assess if 1H MRSI could detect early tumor response to therapy prior to ma

genetic resonance imaging (MRI) changes, and to establish which spectral markers were sensitive to regional changes within and around a heterogeneous tumor mass. A total of 14 patients with lower-grade gliomas were evaluated by multislice 1H MRSI, MRI and clinical examination. Changes associated with chemotherapy were assessed by longitudinal comparisons of regional levels of choline (Cho), N-acetyl-L-aspartate (NAA), and lactate (Lac) relative to total creatine. These changes were, in turn, compared to changes on pre- and post-contrast MR images and to each patient's clinical status. In enhancing tumor regions, there was a significant association between an increase in Lac/Cr during treatment and decreased progression-free survival time. At baseline, a low NAA/Cr in normal-appearing brain tissue adjacent to non-enhancing tumor was associated with decreased progression-free survival time, as was an increase in Cho/Cr during chemotherapy. An increase in Cho/Cr and Lac/Cr in normal-appearing brain regions next to non-enhancing tumor in one patient was noted 2 months before MRI showed progressive disease. These results suggest that 1H MRSI can be a powerful adjunct to MRI in the assessment of tumor response to chemotherapy, and that Cho/Cr and Lac/Cr appear to be the most reliable markers of tumor progression and may predict response prior to MRI changes.

Journal Title: Journal of neuro-oncology

PUBMED ID: 16132503

DOI: doi.org/10.1007/s11060-005-2913-1

Titolo: The efficacy of radiation therapy in the management of grade I astrocytomas.

Autori: Kidd EA., Mansur DB., Leonard JR., Michalski JM., Simpson JR., Perry A.

Data di Pubblicazione: 2005-9-1

Abstract: While this study reports an excellent overall survival, approximately one third of patients with grade I astrocytomas had progressive disease following radiation therapy. In particular, patients with supratentorial tumors and delayed radiation therapy had a worse PFS. Additional investigation is needed to improve the outcome in these patients.

Journal Title: Journal of neuro-oncology

PUBMED ID: 16115932

DOI: doi.org/10.1158/1078-0432.CCR-05-0559

Titolo: Immunologic evaluation of personalized peptide vaccination for patients with advanced malignant glioma.

Autori: Yajima N., Yamanaka R., Mine T., Tsuchiya N., Homma J., Sano M., Kuramoto T., Obata Y., Komatsu N., Arima Y., Yamada A., Shigemori M., Itoh K., Tanaka R.

Data di Pubblicazione: 2005-8-24

Abstract: Personalized peptide vaccinations were recommended for the further clinical study to malignant glioma patients.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 16086097

DOI: doi.org/10.1007/s10637-005-2464-5

Titolo: Pre-irradiation 9-amino [20s] camptothecin (9-AC) in patients with newly diagnosed glioblastoma multiforme.

Autori: Faray D., Ahluwalia MS., Snyder J., Barnett GH., Cohen BH., Suh JH., Peereboom DM.

Data di Pubblicazione: 2005-8-9

Abstract: 9-AC lacks activity against glioblastoma multiforme (GBM). Further studies looking at the efficacy of 9-AC in GBM may be futile.



Journal Title: Investigational new drugs

PUBMED ID: 16078112

DOI: doi.org/10.1007/s11060-005-0603-7

Titolo: HER1/EGFR tyrosine kinase inhibitors for the treatment of glioblastoma multiforme.

Autori: Raizer JJ.

Data di Pubblicazione: 2005-8-4

Abstract: Glioblastoma multiforme (GBM) is a highly malignant brain tumor with limited therapeutic options, a high recurrence rate and mortality. Standard therapy is maximal surgical resection and radiotherapy (RT). Recent data suggest combining temozolomide with RT is better than RT alone. Adjuvant chemotherapy has a modest impact on survival. For relapsed patients there is no standard therapy, but options include chemotherapeutic agents or new agents in development. One approach to improve outcome is using targeted agents that interfere with cell-surface receptors or intracellular signaling pathways. Between 40% and 50% of GBM tumors show HER1/EGFR dysregulation, and almost half co-express the constitutively active mutant receptor subtype EGFRvIII, which may contribute to the aggressive and refractory course of GBM. Numerous studies show a relationship between aberrant HER1/EGFR biology and tumorigenicity in GBM cells. Two available HER1/EGFR tyrosine kinase inhibitors (TKIs) are gefitinib (Iressa) and erlotinib (Tarceva); both show antitumor and radiosensitization effects in vitro and in animal models of GBM. Clinical trials in patients with GBM and other gliomas are ongoing. Preliminary and published results from trials of gefitinib in recurrent GBM show no increased time to progression or overall survival (OS) compared with historical controls. Studies with erlotinib show greater antitumor activity in patients with GBM than with gefitinib, although the impact of both agents on OS remains unclear. GBM treatment with HER1/EGFR TKIs alone or combined with other targeted therapies and conventional modalities deserve further investigation and refinement, as does our understanding of their mechanisms of action and the role of genetics.

Journal Title: Journal of neuro-oncology

PUBMED ID: 16078107

DOI: doi.org/10.1007/s11060-004-3348-9

Titolo: Primary neurocytoma of the spinal cord: a case report and review of literature.

Autori: Sharma S., Sarkar C., Gaikwad S., Suri A., Sharma MC.

Data di Pubblicazione: 2005-8-4

Abstract: Most central neurocytomas (CN) and spinal neurocytomas (SN) have a bland well-differentiated histologic picture and uneventful clinical course. However, rare examples showing histologic atypia, recurrence and even CSF dissemination have been reported. Herein we report a case of recurrent spinal neurocytoma in a 24-year-old male who presented with a 2-month history of weakness and numbness of the left upper and lower limbs, and was previously operated at the same site 10 months ago. MRI revealed a contrast enhancing intramedullary mass involving C5-T1 region. Radiologic and operative impression at both surgeries was that of a glioma, possibly anaplastic. Histologic and immunohistochemical features in both resections were those of an atypical neurocytoma. The tumor showed rare mitoses, focal mild vascular proliferation in both specimens, and necrosis in the initial specimen. MIB1 labeling indices were 9 and 10%, respectively. Based on the analysis of this case and limited data from the literature, it is hypothesized that SN shows a histopathologic picture, immunoprofile and biologic behavior very similar to CN. However, the presence of histologic atypia and increased MIB1 index in SN appear to more closely correlate with tumor recurrence and a worse overall outcome, in part due to their location in the critical region of cervical spinal cord

. Therefore, we hypothesize that SN with atypia requires a close clinical follow up. As in CN, radiation therapy is perhaps best reserved for atypical, progressive and recurrent SN.

Journal Title: Journal of neuro-oncology

PUBMED ID: 16059612

DOI: doi.org/10.1590/s0004-282x2005000300031

Titolo: [Isolated Richter's syndrome in central nervous system: case report]

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Autori: Resende LS., Bacchi CE., Resende LA., Gabarra RC., Niéro-Melo L.

Data di Pubblicazione: 2005-8-2

Abstract: Diffuse large cell non Hodgkin's lymphoma associated with chronic lymphoid leukemia (CLL), or Richter's syndrome, is a rare and serious complication. Isolated Richter's syndrome in the central nervous system is very rare; only 12 cases have been reported. We describe a 74-year-old patient with diffuse large cell non Hodgkin's lymphoma in the right frontal region with the appearance of multiform glioblastoma.

Journal Title: Arquivos de neuro-psiquiatria

PUBMED ID: 16054568

DOI: doi.org/10.1016/S1470-2045(05)70252-7

Titolo: Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children.

Autori: Grill J., Sainte-Rose C., Juvet A., Gentet JC., Lejars O., Frappaz D., Doz F., Rialland X., Pichon F., Bertozzi AI., Chastagner P., Couanet D., Habrand JL., Raquin MA., Le Deley MC., Kalifa C., Kalifa C.

Data di Pubblicazione: 2005-8-2

Abstract: Conventional chemotherapy alone can be used to cure children with non-metastatic medulloblastoma who have gross total resection confirmed by early radiological assessment, but is not sufficient for treatment of those with metastatic or incompletely resected medulloblastoma. Salvage treatment followed by posterior-fossa radiotherapy can effectively treat local relapses or progression.

Journal Title: The Lancet. Oncology

PUBMED ID: 16053669

DOI: doi.org/10.1097/00130404-200505000-00012

Titolo: Thalidomide is inactive in heavily pretreated patients with metastatic breast cancer.

Autori: Morabito A., Carillio G., Longo R., Gasparini G.

Data di Pubblicazione: 2005-8-2

Abstract: Experimental studies have demonstrated that thalidomide has anti-tumor activity mediated by blockage of angiogenesis, with clinical efficacy in multiple myeloma, glioblastoma multiforme, and renal cell cancer. We investigated the therapeutic activity and toxicity of thalidomide in patients with progressive metastatic breast cancer pretreated with chemotherapy. Inclusion criteria were metastatic breast cancer in progression of disease after at least two lines of chemotherapy, age  $\geq$  18 years, performance status  $\leq$  2, and adequate hematologic, renal, and hepatic functions. Twelve patients entered the study, eight of whom were pretreated with three or more lines of chemotherapy (66.7%). Thalidomide was well tolerated: the most common side effects were constipation and somnolence (58.3% of patients). No objective response or durable stable disease was observed. Median time to progression and median overall survival were 8 weeks (range, 4-10 weeks) and 16 weeks (range, 8-54 weeks), respectively. In conclusion, thalidomide is an ineffective treatment in patients with progressive metastatic breast cancer heavily pretreated with chemotherapy.

Journal Title: Cancer journal (Sudbury, Mass.)

PUBMED ID: 16047361

DOI: doi.org/10.1002/pbc.20516

Titolo: Temozolomide in resistant or relapsed pediatric solid tumors.

Autori: De Sio L., Milano GM., Castellano A., Jenkner A., Fidani P., Dominici C., Donfrancesco A.

Data di Pubblicazione: 2005-7-28

Abstract: Oral TMZ was well tolerated in children with resistant or relapsed solid tumors and showed activity in NB and CNS tumours refractory to standard chemotherapy.

Journal Title: Pediatric blood & cancer

PUBMED ID: 16047359

DOI: doi.org/10.1002/pbc.20510

Titolo: Temozolomide and oral VP-16 for children and young adults with recurrent or treatment-induced malignant gliomas.

Autori: Korones DN., Smith A., Foreman N., Bouffet E.

Data di Pubblicazione: 2005-7-28

Abstract: These data suggest there is activity of temozolomide in combination with oral VP-16 for children and young adults with recurrent malignant gliomas.

Journal Title: Pediatric blood & cancer

PUBMED ID: 16033874

DOI: doi.org/10.1093/annonc/mdi317

Titolo: Imatinib and hydroxyurea in pretreated progressive glioblastoma multiforme: a patient series.

Autori: Dresemann G.

Data di Pubblicazione: 2005-7-22

Abstract: The efficacy results, combined with findings that imatinib and hydroxyurea were well tolerated, suggest that this combination shows promise as therapy for GBM.

Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 16000956

DOI: doi.org/10.1097/01.cji.0000162782.86008.ml

Titolo: Phase I trial of intravenous IL-4 pseudomonas exotoxin protein (NBI-3001) in patients with advanced solid tumors that express the IL-4 receptor.

Autori: Garland L., Gitlitz B., Ebbinghaus S., Pan H., de Haan H., Puri RK., Von Hoff D., Figlin R.

Data di Pubblicazione: 2005-7-8

Abstract: NBI-3001 is a novel immunotoxin of attenuated Pseudomonas exotoxin fused to circularly permuted IL-4, which has shown some antitumor effects in glioblastoma multiforme with intratumoral administration. The authors evaluated the safety and tolerability of NBI-3001 administered intravenously in a dose-escalation design to patients with renal cell and non-small cell lung carcinoma whose tumors showed at least 10% IL-4 receptor expression. Cohorts of three to six patients were treated at dose levels of 0.008, 0.016, and 0.027 mg/m<sup>2</sup> daily x 5 days every 28 days. Neutralizing antibody (NAB) titers, plasma levels of NBI-3001, and patient tolerability were monitored sequentially. 14 patients received a total of 36 cycles of NBI-3001 (range 1-6). No dose-limiting toxicities were noted at dose levels 0.008 and 0.016 mg/m<sup>2</sup>. At 0.027 mg/m<sup>2</sup>, two patients developed self-limiting, grade 3 or 4 transaminase elevation during cycle 1. NAB titers of more than 1:100 were detected in five

e of the seven patients treated with at least two cycles; the median titer after cycle 1 and the median maximum titer in subsequent cycles were 1:50 and approximately 1:1,710, respectively. No objective tumor responses were noted. Eight of 12 evaluable patients with renal cell carcinoma had stable disease; four patients had disease progression. High NAB titers resulted in four patients being withdrawn from the study. The dose-limiting toxicity for intravenous NBI-3001 was transaminase elevation at 0.027 mg/m<sup>2</sup>. NBI-3001 at 0.016 mg/m<sup>2</sup> was well tolerated. Low circulating levels of NBI-3001, coupled with rising NAB titers, may have contributed to the lack of response in tumors that express IL-4R.

Journal Title: Journal of immunotherapy (Hagerstown, Md. : 1997)

PUBMED ID: 15998902

DOI: doi.org/10.1200/JCO.2005.23.622

Titolo: Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group Study.

Autori: Galanis E., Buckner JC., Maurer MJ., Kreisberg JI., Ballman K., Boni J., Peralba JM., Jenkins RB., Dakhil SR., Morton RF., Jaeckle KA., Scheithauer BW., Dancey J., Hidalgo M., Walsh DJ., Walsh DJ.

Data di Pubblicazione: 2005-7-7

Abstract: Temsirolimus is well tolerated in recurrent GBM patients. Despite the effect of EIACs on temsirolimus metabolism, therapeutic levels were achieved. Radiographic improvement was observed in 36% of temsirolimus-treated patients, and was associated with significantly longer TTP. High levels of phosphorylated p70s6 kinase in baseline tumor samples appear to predict a patient population more likely to derive benefit from treatment. These findings should be validated in other studies of mTOR inhibitors.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 15971308

DOI: doi.org/10.1016/s0167-8140(04)80012-4

Titolo: Overview of clinical experiences on carbon ion radiotherapy at NIRS.

Autori: Tsujii H., Mizoe JE., Kamada T., Baba M., Kato S., Kato H., Tsuji H., Yamada S., Yasuda S., Ohno T., Yanagi T., Hasegawa A., Sugawara T., Ezawa H., Kandatsu S., Yoshikawa K., Kishimoto R., Miyamoto T.

Data di Pubblicazione: 2005-6-23

Abstract: Carbon ion radiotherapy, due to its physical and biologic advantages over photons, has provided improved outcome in terms of minimized toxicity and high local control rates for locally advanced tumors and pathologically non-squamous cell type of tumors. Using carbon ion radiotherapy, hypofractionated radiotherapy with application of larger doses per fraction and a reduction of overall treatment times as compared to conventional radiotherapy was enabled.

Journal Title: Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology

PUBMED ID: 15930352

DOI: doi.org/10.1158/1078-0432.CCR-05-0120

Titolo: Clinical evaluation of dendritic cell vaccination for patients with recurrent glioma: results of a clinical phase I/II trial.

Autori: Yamanaka R., Homma J., Yajima N., Tsuchiya N., Sano M., Kobayashi T., Yoshida S., Abe T., Narita M., Takahashi M., Tanaka R.

Data di Pubblicazione: 2005-6-3

Abstract: This study showed the safety and clinical response of autologous tumor lysate-pulsed dendritic cell therapy for patients with malignant glioma

. Dendritic cell therapy is recommended for further clinical studies in malignant glioma patients.  
Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 15925999

DOI: doi.org/10.1007/s11060-004-3546-5

Titolo: Primary dissemination of high-grade gliomas in children: experiences from four studies of the Pediatric Oncology and Hematology Society of the German Language Group (GPOH).

Autori: Benesch M., Wagner S., Berthold F., Wolff JE.

Data di Pubblicazione: 2005-6-1

Abstract: Initial diagnostic evaluation should include complete CNS imaging as well as cerebrospinal fluid examination in all patients with HGG. As prognosis of children with HGG and primary CNS dissemination was not inferior to patients without dissemination in our population, these patients should be treated in the same way as patients without primary CNS dissemination.

Journal Title: Journal of neuro-oncology

PUBMED ID: 15918940

DOI: doi.org/10.1227/01.neu.0000159649.71890.30

Titolo: Safety and feasibility of convection-enhanced delivery of Cilastatin for the treatment of malignant glioma: initial experience in 51 patients.

Autori: Patel SJ., Shapiro WR., Laske DW., Jensen RL., Asher AL., Wessels BW., Carpenter SP., Shan JS.

Data di Pubblicazione: 2005-5-28

Abstract: The majority of Cilastatin infusions delivered between 90 and 110% of the prescribed administered activity to the targeted region. This method of administration has an acceptable safety profile compared with literature reports of other therapeutics delivered by convection-enhanced delivery.

Journal Title: Neurosurgery

PUBMED ID: 15912507

DOI: doi.org/10.1002/cncr.21110

Titolo: A multicenter retrospective study of chemotherapy for recurrent intracranial ependymal tumors in adults by the Gruppo Italiano Cooperativo di Neuro-Oncologia.

Autori: Brandes AA., Cavallo G., Reni M., Tosoni A., Nicolardi L., Scopece L., Franceschi E., Sotti G., Talacchi A., Turazzi S., Ermani M.

Data di Pubblicazione: 2005-5-25

Abstract: Cisplatin-based chemotherapy achieved a higher response rate, but did not prolong disease progression-free survival or OS. More active regimens for the salvage treatment of ependymal tumors have yet to be found.

Journal Title: Cancer

PUBMED ID: 15870090

DOI: doi.org/10.1093/annonc/mdi183

Titolo: Neoadjuvant phase II multicentre study of new agents in patients with malignant glioma after minimal surgery. Report of a cohort of 187 patients treated with temozolomide.

Autori: Brada M., Ashley S., Dowe A., Gonsalves A., Huchet A., Pesce G., Reni M., Saran F., Wharram B., Wilkins M., Wilkins P.

Data di Pubblicazione: 2005-5-5

Abstract: The phase II study design of primary chemotherapy in patients with malignant glioma following biopsy alone is feasible and provides an objective method of assessment of efficacy as is currently available. The baseline

data on temozolomide provide a benchmark for assessment of efficacy of other agents and combinations.

Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 15857844

DOI: doi.org/10.1093/annonc/mdi225

Titolo: Temozolomide in combination with BCNU before and after radiotherapy in patients with inoperable newly diagnosed glioblastoma multiforme.

Autori: Barrié M., Couprie C., Dufour H., Figarella-Branger D., Muracciole X., Hoang-Xuan K., Braguer D., Martin PM., Peragut JC., Grisoli F., Chinot O.

Data di Pubblicazione: 2005-4-29

Abstract: The combination of BCNU plus temozolomide as neo-adjuvant therapy in inoperable GBM exhibited promising activity with a good safety profile and warrants further evaluation.

Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 15835103

DOI: doi.org/10.3171/ped.2004.101.2.0159

Titolo: The effects of hydrocephalus on intelligence quotient in children with localized infratentorial ependymoma before and after focal radiation therapy.

Autori: Merchant TE., Lee H., Zhu J., Xiong X., Wheeler G., Phipps S., Boop FA., Sanford RA.

Data di Pubblicazione: 2005-4-20

Abstract: Changes in IQ score before and after radiation treatment are significantly influenced by the extent and treatment of hydrocephalus at the time of diagnosis. Hydrocephalus is an important factor to include when analyzing the effects of treatment. Patients who undergo a second surgery for ependymoma are more likely to require the placement of a CSF shunt ( $p = 0.0001$ ).

Journal Title: Journal of neurosurgery

PUBMED ID: 15831236

DOI: doi.org/10.1215/S1152851704000602

Titolo: Phase 2 study of T138067-sodium in patients with malignant glioma: Trial of the National Cancer Institute of Canada Clinical Trials Group.

Autori: Kirby S., Gertler SZ., Mason W., Watling C., Forsyth P., Aniagolu J., Stagg R., Wright M., Powers J., Eisenhauer EA.

Data di Pubblicazione: 2005-4-16

Abstract: We studied the activity of T138067-sodium in patients with malignant gliomas. T138067-sodium is a unique new chemotherapy agent that inhibits microtubule formation by binding irreversibly and specifically to beta(1), beta(2) and beta(4) isotypes of 3-tubulin, causing cell arrest at G(2)/M and inducing apoptosis. Patients with recurrent anaplastic astrocytoma or glioblastoma multiforme were treated intravenously with 330 mg/m(2) of T138067-sodium weekly. Treatment was continued until the patient experienced either unacceptable toxicity or progressive disease. Patients had to have histologically proven glioma, have bidimensionally measurable disease at least 1 cm x 1 cm, and have received no more than one prior adjuvant chemotherapy. No chemotherapy or radiotherapy for recurrent disease was permitted. Nineteen patients entered the trial. One patient was found to be ineligible. There were two patients with anaplastic astrocytoma and 16 with glioblastoma multiforme. Only two patients had received prior adjuvant chemotherapy. The first seven patients had full pharmacokinetic sampling. No dose-limiting toxicity was seen, and pharmacokinetic results were consistent with those from nonglioma patients. The most common drug-related effects were fatigue (33%), nausea (28%),

neutropenia (28%), and anorexia (17%). No patients stopped the study because of toxicity. No responses were seen in the 15 eligible patients who completed at least one cycle. Three patients had stable disease with a median duration of 2.6 months. Our results suggest that given in this dose and schedule T 138067-sodium does not have activity in this population of anaplastic astrocytoma and glioblastoma multiforme.

Journal Title: Neuro-oncology

PUBMED ID: 15813507

DOI: Mancante

Titolo: Benefit of temozolomide compared to procarbazine in treatment of glioblastoma multiforme at first relapse: effect on neurological functioning, performance status, and health related quality of life.

Autori: Macdonald DR., Kiebert G., Prados M., Yung A., Olson J.

Data di Pubblicazione: 2005-4-9

Abstract: Since high-grade malignant gliomas can seldom be treated curatively, the main aim of first line therapy is to improve progression free survival (PFS), to reduce morbidity, and to preserve, if not restore neurological functions and the capacity to perform daily activities. Focusing on a single clinical efficacy parameter in clinical trials may provide a potentially biased result, as for patients the overall result of treatment entails a more complex picture of weighing and balancing gains and losses on different outcome measures. In this paper we address different clinical outcomes measures separately and we illustrate the value of multiple outcome measures using the results of a recent clinical trial comparing temozolomide with procarbazine in the treatment of Glioblastoma Multiforme. Compared with procarbazine, temozolomide not only prolonged PFS, but also maintained neurological functioning and performance status for a longer period of time, and also improved health-related quality of life (HRQL). All these statistically significant outcomes demonstrate a remarkable consistency. In addition, temozolomide showed a trend of extending overall survival over procarbazine.

Journal Title: Cancer investigation

PUBMED ID: 15805192

DOI: doi.org/10.1073/pnas.0501532102

Titolo: Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response.

Autori: Moffat BA., Chenevert TL., Lawrence TS., Meyer CR., Johnson TD., Dong Q., Tsien C., Mukherji S., Quint DJ., Gebarski SS., Robertson PL., Junck L R., Rehemtulla A., Ross BD.

Data di Pubblicazione: 2005-4-5

Abstract: Assessment of radiation and chemotherapy efficacy for brain cancer patients is traditionally accomplished by measuring changes in tumor size several months after therapy has been administered. The ability to use noninvasive imaging during the early stages of fractionated therapy to determine whether a particular treatment will be effective would provide an opportunity to optimize individual patient management and avoid unnecessary systemic toxicity, expense, and treatment delays. We investigated whether changes in the Brownian motion of water within tumor tissue as quantified by using diffusion MRI could be used as a biomarker for early prediction of treatment response in brain cancer patients. Twenty brain tumor patients were examined by standard and diffusion MRI before initiation of treatment. Additional images were acquired 3 weeks after initiation of chemo- and/or radiotherapy. Images were coregistered to pretreatment scans, and changes in tumor water diffusion values were calculated and displayed as a functional diffusion map (fDM) for correlation with clinical response. Of the 20 patients imaged during the course of therapy, 6 were classified as having a partial response, 6 as stable disease, and 8 as progressive disease. The fDMs were found to predict patient

t response at 3 weeks from the start of treatment, revealing that early changes in tumor diffusion values could be used as a prognostic indicator of subsequent volumetric tumor response. Overall, fDM analysis provided an early biomarker for predicting treatment response in brain tumor patients.  
Journal Title: Proceedings of the National Academy of Sciences of the United States of America

PUBMED ID: 15782008

DOI: doi.org/10.2176/nmc.45.156

Titolo: Primary cerebral angiitis containing marked xanthoma cells with massive intraparenchymal involvement--case report--.

Autori: Ishikawa E., Tsuboi K., Takano S., Kimura H., Aoki T., Mashiko R., Nagata M.

Data di Pubblicazione: 2005-3-23

Abstract: A 27-year-old woman was referred to our hospital with mild disorientation, bilateral abducens nerve palsy, and mild left hemiparesis. Magnetic resonance (MR) imaging revealed diffuse mass lesions resembling malignant glioma in the right frontal intraparenchymal region, with enhancement of multiple meningeal and intraparenchymal nodules. Partial resection of the frontal lesion was performed. Histological examination revealed that the specimens consisted of brain tissue, with marked perivascular infiltration of histiocytes and sheets of xanthomatous cells. The diagnosis was primary cerebral angiitis containing marked xanthoma cells. Steroid therapy was administered over 1 week. MR imaging showed that the remaining lesions resolved gradually, and had disappeared 2 years after surgery. No neurological symptoms or recurrence of the tumor has been observed during the 6-year period since the operation.

Journal Title: Neurologia medico-chirurgica

PUBMED ID: 15770637

DOI: doi.org/10.1002/pbc.20212

Titolo: Ependymal tumors in childhood.

Autori: Agaoglu FY., Ayan I., Dizdar Y., Kebudi R., Gorgun O., Darendeliler E.

Data di Pubblicazione: 2005-3-17

Abstract: The majority of complete responders were patients who had total tumor removal. Treatment failure occurred mainly within the first 2 years, and outcome was dismal for patients who relapsed or had progressive disease. The median age at diagnosis is 6 years in our patient group; younger children (less than 3 years old) have less favorable outcome. There was no significant difference in survival or progression-free survival between the two histologic subtypes.

Journal Title: Pediatric blood & cancer

PUBMED ID: 15737833

DOI: doi.org/10.1016/S1470-2045(05)01767-5

Titolo: MRI in treatment of adult gliomas.

Autori: Henson JW., Gaviani P., Gonzalez RG.

Data di Pubblicazione: 2005-3-2

Abstract: Diffuse astrocytomas of the adult cerebral hemispheres are unique among tumours in human beings in the extent to which their imaging features are related to histopathological characteristics and clinical behaviour. However, understanding is still restricted about the value of imaging features in the measurement of response and of progression in these tumours. The present approach used in clinical trials, which consists of an anatomical measurement of the enhancing tumour on MRI, has many problems, and might not be acceptable as a surrogate endpoint for survival in patients with glioblastoma



who are enrolled in clinical trials. Dynamic imaging techniques, such as capillary permeability mapping, are being used in studies of new drugs that target specific molecular features of gliomas; however, the validity of these techniques has not been elucidated. Diffusion imaging can be valuable for fibre-tract mapping to assist surgical planning and might become useful in measuring early response to treatment in densely cellular tumours. Functional imaging techniques can be used to localise motor, sensory, and language-control areas before surgery. Intraoperative MRI has produced improvements in the extent of tumour resection, and molecular imaging is another technique on the horizon, which could come to have a role in clinical trials in the near future. Thus, as a rapidly expanding sphere of investigation, brain-tumour imaging is producing great excitement. The aim of these new techniques is to aid the identification of more effective treatments.

Journal Title: The Lancet. Oncology

PUBMED ID: 15735921

DOI: doi.org/10.1007/s11060-004-2026-2

Titolo: A Phase II trial of paclitaxel and topotecan with filgrastim in patients with recurrent or refractory glioblastoma multiforme or anaplastic astrocytoma.

Autori: Pipas JM., Meyer LP., Rhodes CH., Cromwell LD., McDonnell CE., Kingman LS., Rigas JR., Fadul CE.

Data di Pubblicazione: 2005-3-1

Abstract: Paclitaxel and topotecan with G-CSF support exhibits modest activity in adults with recurrent or refractory glioblastoma and anaplastic astrocytoma. The significant hematotoxicity encountered, however, cannot justify further investigation of this combination in patients with high grade brain tumors.

Journal Title: Journal of neuro-oncology

PUBMED ID: 15701286

DOI: doi.org/10.1215/S1152851703000589

Titolo: Sustained radiographic and clinical response in patient with bifrontal recurrent glioblastoma multiforme with intracerebral infusion of the recombinant targeted toxin TP-38: case study.

Autori: Sampson JH., Reardon DA., Friedman AH., Friedman HS., Coleman RE., McClendon RE., Pastan I., Bigner DD.

Data di Pubblicazione: 2005-2-11

Abstract: Glioblastoma multiforme remains refractory to conventional therapy, and novel therapeutic modalities are desperately needed. TP-38 is a recombinant chimeric protein containing a genetically engineered form of the cytotoxic Pseudomonas exotoxin fused to transforming growth factor (TGF)-alpha. TGF-alpha binds with high affinity to the epidermal growth factor receptor, which is uniformly overexpressed in malignant gliomas, often because of gene amplification. Prior to therapy with TP-38, the patient described here was completely refractory to multiple other therapies, with radiographic and pathologic evidence of tumor progression. After therapy, she improved clinically, was weaned off steroids and anti-convulsants, and experienced a progressive decrease in enhancing tumor volume. Despite multiple prior recurrences, she has not progressed for >43 months after TP-38 therapy. Small remaining areas of enhancement demonstrate no evidence of tumor histologically and are hypometabolic on positron emission tomography. This report describes a dramatic and sustained clinical and radiographic response in a patient with a bifrontal glioblastoma multiforme treated with intratumoral infusion of a novel targeted toxin, TP-38.

Journal Title: Neuro-oncology

PUBMED ID: 15701281

DOI: doi.org/10.1215/S1152851704000304

Titolo: Sequential chemotherapy, high-dose thiotepa, circulating progenitor cell rescue, and radiotherapy for childhood high-grade glioma.

Autori: Massimino M., Gandola L., Luksch R., Spreafico F., Riva D., Solero C., Giangaspero F., Locatelli F., Podda M., Bozzi F., Pignoli E., Collini P., Cefalo G., Zecca M., Casanova M., Ferrari A., Terenziani M., Meazza C., Polastri D., Scaramuzza D., Ravagnani F., Fossati-Bellani F.

Data di Pubblicazione: 2005-2-11

Abstract: Childhood malignant gliomas are rare, but their clinical behavior is almost as aggressive as in adults, with resistance to therapy, rapid progression, and not uncommonly, dissemination. Our study protocol incorporated sequential chemotherapy and high-dose thiotepa in the preradiant phase, followed by focal radiotherapy and maintenance with vincristine and lomustine for a total duration of one year. The induction treatment consisted of two courses of cisplatin (30 mg/m<sup>2</sup>) plus etoposide (150 mg/m<sup>2</sup>) x 3 days and of vincristine (1.4 mg/m<sup>2</sup>) plus cyclophosphamide (1.5 g/m<sup>2</sup>) plus high-dose methotrexate (8 g/m<sup>2</sup>), followed by high-dose thiotepa (300 mg/m<sup>2</sup> x 3 doses), with harvesting of peripheral blood progenitor cells after the first cisplatin/etoposide course. From August 1996 to March 2003, 21 children, 14 females and 7 males, with a median age of 10 years were enrolled, 18 presenting with residual disease after surgery. Histologies were glioblastoma multiforme in 10, anaplastic astrocytoma in nine, and anaplastic oligodendroglioma in two; sites of origin were supratentorial areas in 17, spine in two, and posterior fossa in two. Of the 21 patients, 12 have died (10 after relapse, with a median time to progression for the whole series of 14 months; one with intratumoral bleeding at 40 months after diagnosis; and one affected by Turcot syndrome for duodenal cancer relapse). Four of 12 relapsed children had tumor dissemination. At a median follow-up of 57 months, overall survival and progression-free survival at four years were 43% and 46%, respectively. Sequential and high-dose chemotherapy can be afforded in front-line therapy of childhood malignant glioma without excessive morbidity and rather encouraging results.

Journal Title: Neuro-oncology

PUBMED ID: 15662767

DOI: Mancante

Titolo: Temozolomide chemotherapy of patients with recurrent anaplastic astrocytomas and glioblastomas.

Autori: Sipos L., Vitanovics D., Afra D.

Data di Pubblicazione: 2005-1-25

Abstract: Temozolomide chemotherapy in patients with recurrent malignant astrocytoma and glioblastoma proved to be efficacious and similar good results were achieved as with a nitrosourea based combined chemotherapy. Even in those patients who received previous chemotherapy temozolomide is well tolerated and a relatively long time to progression was achieved in cases of recurrent malignant gliomas. In a few number of patients where BCNU had been previously failed with temozolomide stable disease was achieved. Temozolomide seems to be a promising drug in the chemotherapy of malignant gliomas and can be applied as a second line chemotherapy, as well.

Journal Title: Idegygyaszati szemle

PUBMED ID: 15611503

DOI: doi.org/10.1200/JCO.2004.12.126

Titolo: Feasibility and response to induction chemotherapy intensified with high-dose methotrexate for young children with newly diagnosed high-risk disseminated medulloblastoma.

Autori: Chi SN., Gardner SL., Levy AS., Knopp EA., Miller DC., Wisoff JH., Weisner HL., Finlay JL.

Data di Pubblicazione: 2004-12-22

Abstract: This intensified induction chemotherapy regimen is feasible and tolerable. With the majority of patients with disseminated medulloblastoma having M2 or M3 disease at diagnosis, the encouraging high response rate of this intensified induction regimen suggests that such an addition of methotrexate should be explored in future studies.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 15570079

DOI: doi.org/10.1200/JCO.2004.06.181

Titolo: Second-line chemotherapy with irinotecan plus carmustine in glioblastoma recurrent or progressive after first-line temozolomide chemotherapy: a phase II study of the Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO)

Autori: Brandes AA., Tosoni A., Basso U., Reni M., Valduga F., Monfardini S., Amistà P., Nicolardi L., Sotti G., Ermani M.

Data di Pubblicazione: 2004-12-1

Abstract: The BCNU plus irinotecan regimen seems active and non-cross-resistant in patients with GBM with recurrence after temozolomide-based chemotherapy.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 15565574

DOI: doi.org/10.1002/cncr.20741

Titolo: Role of temozolomide after radiotherapy for newly diagnosed diffuse brainstem glioma in children: results of a multiinstitutional study (SJHG-98)

Autori: Broniscer A., Iacono L., Chintagumpala M., Fouladi M., Wallace D., Bowers DC., Stewart C., Krasin MJ., Gajjar A.

Data di Pubblicazione: 2004-11-27

Abstract: The administration of temozolomide after RT did not alter the poor prognosis associated with newly diagnosed diffuse brainstem glioma in children.

Journal Title: Cancer

PUBMED ID: 15565548

DOI: doi.org/10.1055/s-2004-832355

Titolo: Low grade chiasmatic-hypothalamic glioma-carboplatin and vincristin chemotherapy effectively defers radiotherapy within a comprehensive treatment strategy -- report from the multicenter treatment study for children and adolescents with a low grade glioma -- HIT-LGG 1996 -- of the Society of Pediatric Oncology and Hematology (GPOH).

Autori: Gnekow AK., Kortmann RD., Pietsch T., Emser A.

Data di Pubblicazione: 2004-11-27

Abstract: Within the comprehensive treatment strategy for low grade glioma HIT-LGG 1996 chemotherapy is effective to delay the need for early radiotherapy in chiasmatic-hypothalamic glioma. More effective reduction of the risk for progression has to be sought for young children < 1 year.

Journal Title: Klinische Padiatrie

PUBMED ID: 15563234

DOI: doi.org/10.2165/00126839-200405060-00002

Titolo: Phase II study of antineoplaston A10 and AS2-1 in children with recurrent and progressive multicentric glioma : a preliminary report.

Autori: Burzynski SR., Weaver RA., Lewy RI., Janicki TJ., Jurida GF., Szymkowski BG., Khan MI., Bestak M.

Data di Pubblicazione: 2004-11-26

Abstract: The results of the present study are favourable in comparison with radiation therapy and chemotherapy. We believe that confirmation of these results through further studies may introduce a new promising treatment for incurable paediatric brain tumours.

Journal Title: Drugs in R&D

PUBMED ID: 15557883

DOI: Mancante

Titolo: Multiple sclerosis and gliomas. Clinical remarks on 10 cases and critical review of the literature.

Autori: Isidori A., Caroli E., Frati A., D'Andrea G., Brogna C., Piccirilli M., Salvati M.

Data di Pubblicazione: 2004-11-24

Abstract: The association between multiple sclerosis and tumours of the central nervous system is unusual. The authors analyzed the clinico-pathological elements of the correlation. The pertinent literature on this subject is critically reviewed. Ten cases of patients with an history of multiple sclerosis for more than 15 years and a clinical and radiological evidence of brain tumour were submitted to surgery in order to remove the lesion and/or to chemotherapy and radiotherapy. The various aspects of the association were studied in detail. A patient with multiple sclerosis, particularly with atypical symptoms, should be evaluated by an annual MRI investigation with intravenous paramagnetic contrast medium. The diagnostic work-up should be: clinical and radiological assessment; MRI in the event of atypical symptoms; Stereotactic or neuronavigation-aided biopsy in any suspected lesions. Patients with multiple sclerosis and glioma present survival times identical to those observed in patients not suffering from multiple sclerosis. The coexistence of multiple sclerosis and brain tumours does not seem to influence the clinical evolution of either of these pathologies. We believe that it is important to achieve an early diagnosis of brain tumour in such patients with a clinical and neuroradiological follow up, so that they can be treated promptly.

Journal Title: Journal of neurosurgical sciences

PUBMED ID: 15509482

DOI: doi.org/10.1007/s11864-004-0037-z

Titolo: Therapeutic strategies for local recurrent malignant glioma.

Autori: Sills AK., Duntsch C., Weimar J.

Data di Pubblicazione: 2004-10-29

Abstract: Patients with local recurrent malignant gliomas present diagnostic and therapeutic challenges for the neuro-oncology practitioner. Management must be individualized depending on the patient's age, performance status, histology, response to initial therapy, type of recurrence (local vs diffuse), and time since original diagnosis. Treatment options may be classified into surgery, additional radiation therapy, or chemotherapy. Results of treatment are often difficult to determine because of limitations of conventional imaging. Symptom palliation is an important goal that often requires additional adjuvant medical therapy. Quality of life issues are also of paramount importance in patients with recurrent malignant glioma and frequently will guide management strategy. Finally, patients with recurrent malignant gliomas should be encouraged to consider participation in a clinical trial in the hopes that better treatment alternatives will be available for this group of patients within the next few years.

Journal Title: Current treatment options in oncology

PUBMED ID: 15477552

DOI: doi.org/10.1212/01.wnl.0000140495.33615.ca

Titolo: How effective is BCNU in recurrent glioblastoma in the modern era? A phase II trial.

Autori: Brandes AA., Tosoni A., Amistà P., Nicolardi L., Grosso D., Berti F., Ermani M.

Data di Pubblicazione: 2004-10-13

Abstract: The activity of this BCNU regimen is comparable with that reported in the past and with the newest therapies, such as temozolomide. However, BCNU toxicity is high and recovery is slow, thus compromising the administration of further drugs in patients with progressive disease.

Journal Title: Neurology

PUBMED ID: 15370616

DOI: doi.org/10.1080/02841860410015271

Titolo: Temozolomide treatment in glioma--experiences in two university hospitals in Finland.

Autori: Mäenpää HO., Aaltonen K., Mäntylä R., Minn H.

Data di Pubblicazione: 2004-9-17

Abstract: Thirty-two patients with relapsing glioma were treated with temozolomide in two university hospitals in Finland. One patient (3%) had complete response and 9 (28%) partial response, with 8 patients (25%) showing stable disease. Median progression-free survival for these 18 patients (56%) was 7 months (range 2-11+). The remaining either had progressive disease (25%) or only clinical evaluation (19%). Karnofsky score improved in 34% of patients and decreased in 3%. Symptoms were alleviated in 44% and deteriorated in 9%. Grade 3-4 toxicity was detected in 9% of the patients. Only 4% of the days in treatment were spent in hospital. An average 1.8 neuroradiological investigations, 6.9 laboratory visits, and 5.3 visits to the oncologist were made. This study confirms that temozolomide has positive effects on the outcome of often heavily pretreated glioma patients. High drug costs are compensated by prolonged home care and even the possibility to maintain working capacity.

Journal Title: Acta oncologica (Stockholm, Sweden)

PUBMED ID: 15332330

DOI: doi.org/10.1023/b:neon.0000033383.84900.c1

Titolo: Multivariate analysis of clinical prognostic factors in children with intracranial ependymomas.

Autori: Jaing TH., Wang HS., Tsay PK., Tseng CK., Jung SM., Lin KL., Lui TN.

Data di Pubblicazione: 2004-8-31

Abstract: The optimal postoperative management of pediatric intracranial ependymomas is controversial. We analyzed clinical prognostic factors for their influence on outcome in such children. Our retrospective series included 15 with supratentorial and 28 with infratentorial tumors. Twenty ependymomas were grade II, and 23 were anaplastic. Complete resection was performed in 18 patients, incomplete resection in 19, and stereotactic biopsy in 6. Radiotherapy was done in 31 patients and chemotherapy in 13. The surviving patients have been followed 8-232 months (median: 69 months). The median survival time was 30 months, and 5-year overall survival and progression-free survival rates were 53.9% and 45.9%, respectively. By tumor site: supratentorial, 56.6% and 50.9%; infratentorial, 52.3% and 42.5%. Multivariate analysis identified complete resection (5-year progression-free survival, 71.8%) and age <3 years old as significant favorable and adverse prognostic features (relative risk, 2.59; 95% CI, 1.05-6.38), respectively. Twenty-six children relapsed 1-107 months after diagnosis (median: 12 months). Relapses were local in 22 cases, and combined local and distant in three cases. Only one of 15 patients with supratentorial tumors developed isolated spinal metastasis. Failure at the primary site is the major obstacle to improve cure rates. The extent of

surgical resection and age were the only statistically significant prognostic factors.

Journal Title: Journal of neuro-oncology

PUBMED ID: 15323467

DOI: doi.org/10.3171/foc.2003.15.5.10

Titolo: Stereotactic radiosurgery for hemangiomas and ependymomas of the spinal cord.

Autori: Ryu SI., Kim DH., Chang SD.

Data di Pubblicazione: 2004-8-25

Abstract: Stereotactic radiosurgery for intramedullary spinal tumors is feasible and safe in selected cases and may prove to be another therapeutic option for these challenging lesions.

Journal Title: Neurosurgical focus

PUBMED ID: 15306839

DOI: doi.org/10.1038/sj.gt.3302336

Titolo: Safety and biodistribution studies of an HSV multigene vector following intracranial delivery to non-human primates.

Autori: Wolfe D., Niranjana A., Trichel A., Wiley C., Ozuer A., Kanal E., Kondziolka D., Krisky D., Goss J., Deluca N., Murphey-Corb M., Glorioso JC.

Data di Pubblicazione: 2004-8-13

Abstract: Malignant glioma is a fatal human cancer in which surgery, chemotherapy and radiation therapies are ineffective. Therapeutic gene transfer used in combination with current treatment methods may augment their effectiveness with improved clinical outcome. We have shown that NUREL-C2, a replication-defective multigene HSV-based vector, is effective in treating animal models of glioma. Here, we report safety and biodistribution studies of NUREL-C2 using rhesus macaques as a model host. Increasing total doses ( $1 \times 10^7$  to  $1 \times 10^9$ ) plaque forming units (PFU) of NUREL-C2 were delivered into the cortex with concomitant delivery of ganciclovir (GCV). The animals were evaluated for changes in behavior, alterations in blood cell counts and chemistry. The results showed that animal behavior was generally unchanged, although the chronic intermediate dose animal became slightly ataxic on day 12 postinjection, a condition resolved by treatment with aspirin. The blood chemistries were unremarkable for all doses. At 4 days following vector injections, magnetic resonance imaging showed inflammatory changes at sites of vector injections concomitant with HSV-TK and TNF $\alpha$  expression. The inflammatory response was reduced at 14 days, resolving by 1 month postinjection, a time point when transgene expression also became undetectable. Immunohistochemical staining following animal killing showed the presence of a diffuse low-grade gliosis with infiltrating macrophages localized to the injection site, which also resolved by 1 month postinoculation. Viral antigens were not detected and injected animals did not develop HSV-neutralizing antibodies. Biodistribution studies revealed that vector genomes remained at the site of injection and were not detected in other tissues including contralateral brain. We concluded that intracranial delivery of  $1 \times 10^9$  PFU NUREL-C2, the highest anticipated patient dose, was well tolerated and should be suitable for safety testing in humans.

Journal Title: Gene therapy

PUBMED ID: 15277636

DOI: doi.org/10.1212/01.wnl.0000130249.41341.58

Titolo: Chemotherapy as initial treatment in gliomatosis cerebri: results with temozolomide.

Autori: Levin N., Gomori JM., Siegal T.

Data di Pubblicazione: 2004-7-28

Abstract: The optimal therapy for gliomatosis cerebri is unclear, and the rate of response to chemotherapy is not known. Eleven radiotherapy-naïve patients received a median number of 10 treatment cycles of temozolomide. An objective response was documented in 45%, and the median time to tumor progression was 13 months with a progression-free survival of 55% at 12 months. These results indicate that radiotherapy to extensive brain regions can be deferred until progressive disease is observed.

Journal Title: Neurology

PUBMED ID: 15277619

DOI: doi.org/10.1212/01.wnl.0000129985.39973.e4

Titolo: Initial chemotherapy in gliomatosis cerebri.

Autori: Sanson M., Cartalat-Carel S., Taillibert S., Napolitano M., Djafari L., Cougnard J., Gervais H., Laigle F., Carpentier A., Mokhtari K., Taillandier L., Chinot O., Duffau H., Honnorat J., Hoang-Xuan K., Delattre JY., Delattre JY.

Data di Pubblicazione: 2004-7-28

Abstract: Initial chemotherapy is useful for some patients with gliomatosis cerebri. Temozolomide is well tolerated and appears to be a valuable alternative to procarbazine-CCNU-vincristine, especially for those with slow-growing, low-grade GC.

Journal Title: Neurology

PUBMED ID: 15241528

DOI: doi.org/10.1007/s00066-004-1221-6

Titolo: Immediate postoperative radiotherapy or "watch and wait" in the management of adult low-grade glioma?

Autori: Kortmann RD., Jeremic B., Weller M., Lutterbach J., Paulsen F., Bamberg M.

Data di Pubblicazione: 2004-7-9

Abstract: The arguments for immediate postoperative irradiation include: low-grade gliomas respond to radiotherapy; the tumors often display an aggressive pathobiological behavior; patients with high risk profile may benefit from immediate radiotherapy in terms of progression-free and overall survival; modern focal radiotherapy is far less toxic than feared; radiotherapy might be more effective at diagnosis than at progression. Chemotherapy might be an alternative in immediate postoperative treatment. Its role, however, is unclear. The forthcoming prospective trial of the EORTC will address this issue in a randomized setting.

Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 15184628

DOI: doi.org/10.1212/01.wnl.0000127617.89363.84

Titolo: One week on/one week off: a novel active regimen of temozolomide for recurrent glioblastoma.

Autori: Wick W., Steinbach JP., Küker WM., Dichgans J., Bamberg M., Weller M.

Data di Pubblicazione: 2004-6-9

Abstract: Twenty-one patients with recurrent or progressive glioblastoma were enrolled in a prospective phase II trial to determine the safety and efficacy of a 1-week on/1-week off regimen of temozolomide administered at 150 mg/m<sup>2</sup> on days 1 to 7 and days 15 to 21 of 28-day treatment cycles. Two patients achieved a partial response (10%), and 17 patients (81%) had stable disease. The median progression-free survival was 5 months. The progression-free survival at 6 months was 48%.

Journal Title: Neurology

PUBMED ID: 15174520

DOI: doi.org/10.1023/b:neon.0000024744.16031.e9

Titolo: Results of contemporary surgical management of radiation necrosis using frameless stereotaxis and intraoperative magnetic resonance imaging.

Autori: McPherson CM., Warnick RE.

Data di Pubblicazione: 2004-6-4

Abstract: In this review, frameless stereotaxis was helpful in guiding the surgeon; however, IOMRI did not provide any additional benefit for the surgical treatment of radiation necrosis. Surgical treatment of radiation necrosis was associated with high risks of complication or neurologic deficit. Given the success of medical therapies, including hyperbaric oxygen, we believe that surgical treatment of radiation necrosis should be reserved for symptomatic patients in whom medical therapy has failed.

Journal Title: Journal of neuro-oncology

PUBMED ID: 15153843

DOI: doi.org/10.1177/107327480401100307

Titolo: Recent progress in immunotherapy for malignant glioma: treatment strategies and results from clinical trials.

Autori: Ehtesham M., Black KL., Yu JS.

Data di Pubblicazione: 2004-5-22

Abstract: An effective treatment paradigm for malignant gliomas may eventually require a multifaceted approach combining two or more different immunotherapeutic strategies. Such scenarios may involve the use of local cytokine gene therapy to enhance glioma-cell immunogenicity in conjunction with dendritic cell-based active vaccination to stimulate systemic tumoricidal T-cell immunity. Given the heterogeneity of this disease process and the potential risk of immunoediting out a selected, treatment-refractory tumor cell population, the concurrent use of multiple modalities that target disparate tumor characteristics may be of greatest therapeutic relevance.

Journal Title: Cancer control : journal of the Moffitt Cancer Center

PUBMED ID: 15140402

DOI: doi.org/10.1593/neo.03349

Titolo: Pretreatment prediction of brain tumors' response to radiation therapy using high b-value diffusion-weighted MRI.

Autori: Mardor Y., Roth Y., Ochershvilli A., Spiegelmann R., Tichler T., Daniels D., Maier SE., Nissim O., Ram Z., Baram J., Orenstein A., Pfeffer R.

Data di Pubblicazione: 2004-5-14

Abstract: Diffusion-weighted magnetic resonance imaging (DWMRI) is sensitive to tissues' biophysical characteristics, including apparent diffusion coefficients (ADCs) and volume fractions of water in different populations. In this work, we evaluate the clinical efficacy of DWMRI and high diffusion-weighted magnetic resonance imaging (HDWMRI), acquired up to  $b = 4000 \text{ sec/mm}^2$  to amplify sensitivity to water diffusion properties, in pretreatment prediction of brain tumors' response to radiotherapy. Twelve patients with 20 brain lesions were studied. Six ring-enhancing lesions were excluded due to their distinct diffusion characteristics. Conventional and DWMRI were acquired on a 0.5-T MRI. Response to therapy was determined from relative changes in tumor volumes calculated from contrast-enhanced T1-weighted MRI, acquired before and a mean of 46 days after beginning therapy. ADCs and a diffusion index,  $R(D)$ , reflecting tissue viability based on water diffusion were calculated from DWMRIs. Pretreatment values of ADC and  $R(D)$  were found to correlate significantly with later tumor response/nonresponse ( $r = 0.76$ ,  $P < .002$  and  $r = 0.77$ ,  $P < .001$ ). This correlation implies that tumors with low pretreatment diffusion values, indicating high viability, will respond better to radiotherapy.



than tumors with high diffusion values, indicating necrosis. These results demonstrate the feasibility of using DWMRI for pretreatment prediction of response to therapy in patients with brain tumors undergoing radiotherapy.

Journal Title: Neoplasia (New York, N.Y.)

PUBMED ID: 15139066

DOI: doi.org/10.1002/cncr.20224

Titolo: Phase II study of temozolomide without radiotherapy in newly diagnosed glioblastoma multiforme in an elderly populations.

Autori: Chinot OL., Barrie M., Frauger E., Dufour H., Figarella-Branger D., Palmari J., Braguer D., Hoang-Xuan K., Moktari K., Peragut JC., Martin PM., Grisoli F.

Data di Pubblicazione: 2004-5-13

Abstract: Temozolomide represents a safe, easily administered, and effective therapeutic approach for elderly patients with newly diagnosed GBM.

Journal Title: Cancer

PUBMED ID: 15093907

DOI: doi.org/10.1016/j.ijrobp.2003.10.040

Titolo: Importance of baseline mini-mental state examination as a prognostic factor for patients with low-grade glioma.

Autori: Brown PD., Buckner JC., O'Fallon JR., Iturria NL., O'Neill BP., Brown CA., Scheithauer BW., Dinapoli RP., Arusell RM., Curran WJ., Abrams R., Shaw EG., Shaw EG., Shaw EG.

Data di Pubblicazione: 2004-4-20

Abstract: The presence of an abnormal baseline MMSE score was a strong predictor of poorer progression-free and overall survival for patients with a low-grade glioma. The baseline MMSE should be considered in future prognostic scoring systems.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 15073866

DOI: doi.org/10.1002/cncr.20168

Titolo: Oral topotecan in children with recurrent or progressive high-grade glioma: a Phase I/II study by the German Society for Pediatric Oncology and Hematology.

Autori: Wagner S., Erdlenbruch B., Längler A., Gnekow A., Kühl J., Albani M., Völpel S., Bucsky P., Emser A., Peters O., Wolff JE.

Data di Pubblicazione: 2004-4-10

Abstract: Oral topotecan (median dose, 0.9 mg/m<sup>2</sup> per day) administered once daily was well tolerated and somewhat effective in children with recurrent high-grade glioma. A schedule in which the daily dose is split so that dosing is performed twice daily may be superior to the current schedule.

Journal Title: Cancer

PUBMED ID: 15073253

DOI: Mancante

Titolo: PET and SPECT for detection of tumor progression in irradiated low-grade astrocytoma: a receiver-operating-characteristic analysis.

Autori: Henze M., Mohammed A., Schlemmer HP., Herfarth KK., Hoffner S., Haufe S., Mier W., Eisenhut M., Debus J., Haberkorn U.

Data di Pubblicazione: 2004-4-10

Abstract: (123)I-IMT SPECT imaging of amino acid transport accurately detects tumor progression in patients with irradiated LGA. In contrast to (123)I-IMT, (18)F-FDG PET was slightly less accurate for classification, and (99m)Tc-MIBI SPECT was of limited value. Imaging of amino acid transport with (123)

I-IMT is a valuable additional tool for the follow-up of LGA, allowing early, noninvasive differentiation of lesions with ambiguous morphology after irradiation.

Journal Title: Journal of nuclear medicine : official publication, Society of Nuclear Medicine

PUBMED ID: 15022289

DOI: doi.org/10.1002/cncr.20072

Titolo: Salvage chemotherapy with cyclophosphamide for recurrent, temozolomide-refractory glioblastoma multiforme.

Autori: Chamberlain MC., Tsao-Wei DD.

Data di Pubblicazione: 2004-3-17

Abstract: CYC exhibited modest efficacy with acceptable toxicity in the current cohort of adult patients with recurrent glioblastoma multiforme, all of whom had previously experienced treatment failure after temozolomide chemotherapy.

Journal Title: Cancer

PUBMED ID: 15022287

DOI: doi.org/10.1002/cncr.20073

Titolo: Pegylated liposomal doxorubicin-efficacy in patients with recurrent high-grade glioma.

Autori: Hau P., Fabel K., Baumgart U., Rümmele P., Grauer O., Bock A., Dietmaier C., Dietmaier W., Dietrich J., Dudel C., Hübner F., Jauch T., Drechsel E., Kleiter I., Wismeth C., Zellner A., Brawanski A., Steinbrecher A., Mariehagen J., Bogdahn U.

Data di Pubblicazione: 2004-3-17

Abstract: Pegylated liposomal doxorubicin administered alone or in combination with tamoxifen is safe and moderately effective in patients with recurrent high-grade glioma. None of the putative predictors for response that were evaluated proved to be significant in this setting.

Journal Title: Cancer

PUBMED ID: 15015788

DOI: doi.org/10.1023/b:neon.0000013479.64348.69

Titolo: Phase II trial of cisplatin plus temozolomide, in recurrent and progressive malignant glioma patients.

Autori: Silvani A., Eoli M., Salmaggi A., Lamperti E., Maccagnano E., Broggi G., Boiardi A.

Data di Pubblicazione: 2004-3-16

Abstract: We report a phase II trial of cisplatin and temozolomide (TMZ) combination in recurrent malignant glioma patients. The DNA repair protein O(6)-alkylguanine-DNA alkyltransferase (AGAT) is important in glioblastoma resistance to alkylating antitumor agents. In vitro, cisplatin (CDDP) decreases MGMT activity in a time- and dose-dependent manner. Thirty-three recurrent malignant glioma patients (20 GBM-13 AA) were treated at recurrence or progression with a CDDP and TMZ association. On days 1 and 2, iv CDDP (40 mg/sqm) was administered. TMZ (at the dose of 200 mg/sqm) was administered as a single oral daily-dose on days 2-6 (starting 24 h after the first CDDP dose), the cycle was repeated every 4 weeks. All patients had been previously treated with surgery followed by radiotherapy and CDDP + BCNU chemotherapy. The primary endpoint of the study was progression free survival at 6 months (PFS-6). Secondary endpoints included radiological response and toxicities. Thirty-three patients received a total of 113 courses (median 3 range 1-11). Complete responses were not observed, partial responses were 18.8% with an additional 39.9% of stable disease. For the whole group of patients the PFS at 6 and 12 months was 52% and 15% with a median TTP of 33 weeks. PFS-6 for GBM and Anap

lastic astrocytoma (AA) were 35% and 69%, respectively. PFS-12 for GBM and A were 13.8% and 17.3%, respectively. Median TTP was 21.3 and 39.5 weeks, respectively. The principal toxic effects of the regimen were: neutropenia (5 WHO grade IV), thrombocytopenia (4 WHO grade IV), nausea and vomiting.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 15015785  
DOI: doi.org/10.1023/b:neon.0000013472.50749.84  
Titolo: The efficacy of stereotactic radiosurgery in the management of intracranial ependymoma.  
Autori: Mansur DB., Drzymala RE., Rich KM., Klein EE., Simpson JR.  
Data di Pubblicazione: 2004-3-16  
Abstract: SRS is an effective treatment for intracranial ependymoma. Further clinical trials are warranted incorporating radiosurgery as a component of initial management in selected ependymoma patients.  
Journal Title: Journal of neuro-oncology

PUBMED ID: 14770438  
DOI: doi.org/10.1002/cncr.20042  
Titolo: Second-line treatment with carboplatin for recurrent or progressive oligodendroglial tumors after PCV (procarbazine, lomustine, and vincristine) chemotherapy: a phase II study.  
Autori: Soffietti R., Nobile M., Rudà R., Borgognone M., Costanza A., Laguzzi E., Mutani R.  
Data di Pubblicazione: 2004-2-11  
Abstract: When administered according to a monthly schedule, carboplatin exhibited modest activity in adult patients with recurrent or progressive oligodendroglioma or oligoastrocytoma who experienced treatment failure after PCV chemotherapy; the current treatment regimen also was associated with severe toxicity. Further improvement of second-line chemotherapy for the patient group examined in the current study is necessary.  
Journal Title: Cancer

PUBMED ID: 14745879  
DOI: doi.org/10.1002/cncr.11949  
Titolo: Temozolomide in the treatment of recurrent malignant glioma.  
Autori: Chang SM., Theodosopoulos P., Lamborn K., Malec M., Rabbitt J., Page M., Prados MD.  
Data di Pubblicazione: 2004-1-28  
Abstract: Temozolomide was well tolerated in patients with recurrent malignant glioma and had modest efficacy, even at the time of multiple recurrences.  
Journal Title: Cancer

PUBMED ID: 14734866  
DOI: doi.org/10.1159/000075260  
Titolo: Surgical outcome following resection of contrast-enhanced pediatric brainstem gliomas.  
Autori: Lesniak MS., Klem JM., Weingart J., Carson BS.  
Data di Pubblicazione: 2004-1-22  
Abstract: This case series illustrates that contrast-enhanced MRI has positive prognostic value in the management of pediatric brainstem gliomas. In our study, the majority of enhancing tumors were low grade and amenable to surgical intervention. Consequently, we recommend surgical resection and pathological diagnosis of all enhancing brainstem tumors with adjuvant therapy reserved for recurrent or unresectable cases.  
Journal Title: Pediatric neurosurgery

PUBMED ID: 14682377

DOI: doi.org/10.1023/b:neon.00000003588.18644.9c

Titolo: Treatment of progressive or recurrent glioblastoma multiforme in adults with herpes simplex virus thymidine kinase gene vector-producer cells followed by intravenous ganciclovir administration: a phase I/II multi-institutional trial.

Autori: Prados MD., McDermott M., Chang SM., Wilson CB., Fick J., Culver KW., Van Gilder J., Keles GE., Spence A., Berger M.

Data di Pubblicazione: 2003-12-20

Abstract: To determine the safety and evaluate the efficacy of repeated administration of virus-producing cells (GLI 328) containing the herpes simplex virus thymidine-kinase gene followed by ganciclovir treatment in adults with recurrent glioblastoma multiforme, we conducted a phase I/II multi-institutional trial. Eligible patients underwent surgical resection of tumor, followed by injections of vector producing cells (VPC) into the brain adjacent to the cavity. An Ommaya reservoir placed after surgery was used to inject a further dose of VPC seven days after surgery, followed seven days later by ganciclovir. Further gene therapy was given at 28-day intervals for up to a total of five cycles. Toxicity and anti-tumor effect were assessed. Of 30 patients who enrolled in the study, 16 experienced serious adverse events possibly related to the experimental therapy. Laboratory testing, including polymerase chain reaction analysis to detect replication-competent retrovirus in peripheral blood lymphocytes and tissues, as well as co-cultivation bioassays, were negative. Before receiving ganciclovir, 37% of the patients showed evidence of transduced peripheral blood leukocytes, but only 12% showed a persistence of transduced cells at the end of the first cycle of ganciclovir. Median survival was 8.4 months. Twenty percent of the patients (n = 6) survived more than 12 months from the date of study entry. This treatment modality is feasible and appears to have some evidence of efficacy. Toxicity may be related in part to the method of gene delivery.

Journal Title: Journal of neuro-oncology

PUBMED ID: 14666736

DOI: Mancante

Titolo: Recombinant mutant human tumor necrosis factor-alpha (TNF-SAM2) immunotherapy with ranimustine chemotherapy and concurrent radiation therapy for malignant astrocytomas.

Autori: Fukushima T., Yamamoto M., Oshiro S., Tsugu H., Hirakawa K., Soma G.

Data di Pubblicazione: 2003-12-12

Abstract: These results suggest that combined chemotherapy with mutant TNF-alpha (TNF-SAM2) in this patient population seems to be safe and tolerable and may benefit those with anaplastic astrocytoma. These intriguing clinical observations warrant further evaluation to determine whether this approach can provide therapeutic benefits and improve survival.

Journal Title: Anticancer research

PUBMED ID: 14630676

DOI: doi.org/10.1093/annonc/mdg494

Titolo: Carboplatin and teniposide as third-line chemotherapy in patients with recurrent oligodendroglioma or oligoastrocytoma: a phase II study.

Autori: Brandes AA., Basso U., Vastola F., Tosoni A., Pasetto LM., Jirillo A., Lonardi S., Paris MK., Koussis H., Monfardini S., Ermani M.

Data di Pubblicazione: 2003-11-25

Abstract: Although the response rate of combined carboplatin and teniposide chemotherapy in heavily pretreated oligodendroglial tumors is moderate, the

toxicity is manageable, and delay of progression in responders or stable patients may still confer a relevant clinical benefit.  
Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 14630675

DOI: doi.org/10.1093/annonc/mdg502

Titolo: Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response.

Autori: Pace A., Vidiri A., Galiè E., Carosi M., Telera S., Cianciulli AM., Canalini P., Giannarelli D., Jandolo B., Carapella CM.

Data di Pubblicazione: 2003-11-25

Abstract: The high response rate of 47% (95% CI 31% to 61%) confirms that TMZ chemotherapy is a valid option in the treatment of progressive LGG. The present preliminary results seem interesting and warrant further evaluation of TMZ clinical activity in a larger series of progressive LGG.

Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 14630674

DOI: doi.org/10.1093/annonc/mdg371

Titolo: Phase II study of primary temozolomide chemotherapy in patients with WHO grade II gliomas.

Autori: Brada M., Viviers L., Abson C., Hines F., Britton J., Ashley S., Sardell S., Traish D., Gonsalves A., Wilkins P., Westbury C.

Data di Pubblicazione: 2003-11-25

Abstract: Temozolomide has single-agent activity in patients with WHO grade II cerebral glioma, with modest improvement in quality of life and improvement in epilepsy control. On present evidence, temozolomide cannot be considered as primary therapy without formal comparison with other treatment modalities.

Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 14558604

DOI: doi.org/10.1023/a:1025689004046

Titolo: Loss of heterozygosity for loci on chromosome arms 1p and 10q in oligodendroglial tumors: relationship to outcome and chemosensitivity.

Autori: Thiessen B., Maguire JA., McNeil K., Huntsman D., Martin MA., Horsman D.

Data di Pubblicazione: 2003-10-16

Abstract: Oligodendroglial tumors frequently have deletions of chromosomal loci on 1p and 19q. Loss of heterozygosity (LOH) of chromosome 10 may be a negative prognostic factor. We reviewed 23 patients with oligodendroglial tumors, to evaluate the frequency of 1p and 10q LOH and correlate with clinical outcome. Three loci (D1S402, D1S1172, MCT118) on 1p and 2 loci (D10S520 and D10S521) on 10q were analyzed for LOH using PCR techniques. Sixteen oligodendrogliomas (6 low grade and 10 anaplastic) and 7 oligoastrocytomas (1 low grade and 6 anaplastic) were studied. Overall 14/22 (64%) showed 1p LOH and 7/23 (30%) showed 10q LOH. Of 7 patients with some response to chemotherapy, all showed 1p LOH and none had 10q LOH. Of 5 patients with stable or progressive disease, 1 had 1p LOH and 2 showed 10q LOH. The presence of 1p LOH was significantly associated with response to chemotherapy ( $p = 0.02$ ). Median progression free survival (PFS) was 31 months for 1p intact patients and 118 months for the 1p LOH group ( $p = 0.014$ ). Median PFS for 10q LOH patients was 31 and 118 months for patients with intact chromosome 10 ( $p = 0.016$ ). 1p LOH is a predictor of response to chemotherapy and a good prognostic factor. 10q LO

H is less common in oligodendroglial tumors but predicts for worse outcome. Molecular genotyping of oligodendroglial tumors is recommended as part of the standard diagnostic workup.

Journal Title: Journal of neuro-oncology

PUBMED ID: 14509949

DOI: doi.org/10.1007/s00066-003-9104-9

Titolo: Current and future strategies in radiotherapy of childhood low-grade glioma of the brain. Part I: Treatment modalities of radiation therapy.

Autori: Kortmann RD., Timmermann B., Taylor RE., Scarzello G., Plasswilm L., Paulsen F., Jeremic B., Gnekow AK., Dieckmann K., Kay S., Bamberg M.

Data di Pubblicazione: 2003-9-27

Abstract: Radiation therapy is an effective treatment modality in children with low-grade glioma regarding tumor control and improvement and/or preservation of neurologic function or vision, respectively. More prospective studies are needed to address the impact of modern radiation therapy technologies (including intensity-modulated radiotherapy) on outcome especially in the very young and to define the role of radiation therapy as a part of a comprehensive treatment approach. The forthcoming prospective trial SIOP/GPOH LGG RT 2003 is addressing this issue.

Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 12959854

DOI: doi.org/10.1080/08880010390232709

Titolo: Chemotherapy for progressive low-grade gliomas in children older than ten years: the Dana-Farber experience.

Autori: Heath JA., Turner CD., Poussaint TY., Scott RM., Goumnerova L., Kieran MW.

Data di Pubblicazione: 2003-9-10

Abstract: The purpose of this retrospective study was to examine the clinical and radiographic response rates to and toxicity of chemotherapy for low-grade gliomas in children older than 10 years of age. Between June 1999 and January 2001, seven consecutive children between the ages of 10 and 18 were treated with vincristine and carboplatin +/- thioguanine, procarbazine, CCNU [lomustine], and vincristine (TPCV) for progressive low-grade gliomas. All 7 children completed a 10-week induction course of vincristine and carboplatin; 3 were switched to TPCV during the maintenance phase of therapy after developing an allergic reaction to carboplatin. Overall, 4 patients had a radiographic response to treatment with chemotherapy (3 partial responses and 1 minor response: objective response rate of 57%), and 2 more showed stable disease. One patient progressed while on treatment and 1 patient progressed off treatment, and after 31 months had elapsed. The resulting progression-free survival at the time of this report was 71%. The median duration of follow-up was 32 months (range 25-42 months). Hematologic toxicity was common, but did not result in cessation of therapy. No other significant treatment-related toxicities were observed. The results suggest that the clinical response/disease stabilization rate in children older than 10 years of age does not differ markedly from that observed in younger children. A prospective clinical trial of chemotherapy for progressive low-grade gliomas in children older than 10 years is therefore warranted.

Journal Title: Pediatric hematology and oncology

PUBMED ID: 12884791

DOI: Mancante

Titolo: [Therapeutic efficacy and prognostic factors in diffuse astrocytomas].

Autori: Watanabe T., Komine C., Yokoyama T., Yoshino A., Katayama Y.

Data di Pubblicazione: 2003-7-30

Abstract: Diffuse astrocytomas are slowly growing tumors with a relatively long overall survival. Considerable controversy exists as to the best therapeutic management for patients with such tumors. In the present study, we retrospectively analyzed a series of 64 patients with WHO grade II astrocytomas of the cerebral hemispheres. Gross total resection and interferon-beta therapy were significantly associated with both longer progression free survival (PFS) and overall survival (OS). Immediate postoperative radiation therapy did not prolong either the PFS or OS. The presence of promoter hypermethylation of the O6-methylguanine-DNA methyltransferase (MGMT) gene was an independent predictor of a shorter PFS. Our data suggest that radical surgery plus interferon-beta therapy may offer the best chance for long survival. Since the presence of MGMT methylation is a probable indication of an increased sensitivity to alkylating chemotherapeutic agents, determining the methylation status of MGMT could provide a potential basis for logical therapeutic intervention in identifying a subgroup of patients who could be candidates for early chemotherapy.

Journal Title: No shinkei geka. Neurological surgery

PUBMED ID: 12829152

DOI: doi.org/10.1016/s0360-3016(03)00293-1

Titolo: Gliomatosis cerebri: improved outcome with radiotherapy.

Autori: Perkins GH., Schomer DF., Fuller GN., Allen PK., Maor MH.

Data di Pubblicazione: 2003-6-28

Abstract: RT is effective against gliomatosis cerebri. Patients who are young and have a nonglioblastoma tumor histologic subtype perform more favorably. In this analysis, no role for chemotherapy, extensive surgery, or whole-brain RT was found.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 12805331

DOI: doi.org/10.1200/JCO.2003.12.097

Titolo: Phase II evaluation of temozolomide and 13-cis-retinoic acid for the treatment of recurrent and progressive malignant glioma: a North American Brain Tumor Consortium study.

Autori: Jaeckle KA., Hess KR., Yung WK., Greenberg H., Fine H., Schiff D., Pollack IF., Kuhn J., Fink K., Mehta M., Cloughesy T., Nicholas MK., Chang S., Prados M., Prados M.

Data di Pubblicazione: 2003-6-14

Abstract: TMZ and cRA were active, exceeding our 20% thresholds for PFS 6 success, assuming 20% improvement over our previously reported database (glioblastoma multiforme: expected, 30%; observed, 32%; anaplastic glioma: expected, 40%; observed, 50%).

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 12778010

DOI: doi.org/10.1097/00001622-200305000-00002

Titolo: The role of gamma knife radiosurgery in the treatment of primary and metastatic brain tumors.

Autori: Gerosa M., Nicolato A., Foroni R.

Data di Pubblicazione: 2003-6-5

Abstract: With the widespread diffusion of stereotactic radiosurgical procedures, GKR treatments have gained considerable momentum as a major therapeutic option for patients harboring primary or metastatic brain tumors. Present results in high grade gliomas indicate a potential palliative role of this t

technique. The overall low radiosensitivity of these oncotypes and their infiltrative nature-with the resulting problems in properly defining the tumor target-are still a major obstacle to further development of the approach. In this regard, useful contributions are expected from advances in molecular neurobiology and functional neuroimaging as shown by preliminary investigations with MR spectroscopy. Surgery maintains a dominant role in the therapeutic armamentarium for low grade gliomas. However, in unfavorable cases (unresectable tumors, recurrences), GKR seems to be an effective alternative to conventional radiochemotherapy. In grade 2 astrocytomas and specifically in grade 1 pilocytic forms, short-to-mid-term reported studies have documented encouraging 70 to 93% local tumor control rates, with minimal cerebral toxicity. Finally, during the last decade, GKR has become a primary treatment choice for patients harboring small-to-medium-size brain metastases, with reasonable life expectancy and no impending intracranial hypertension. Focal tumor responses are consistently elevated, even in the most radioresistant oncotypes (melanoma, renal carcinoma); median and actuarial survival rates are far better than with conventional radiation treatments and are comparable to those observed in accurately selected surgical-radiation series.

Journal Title: Current opinion in oncology

PUBMED ID: 12744471

DOI: doi.org/10.1111/j.1750-3639.2003.tb00017.x

Titolo: Promoter hypermethylation of the DNA repair gene O6-methylguanine-DNA methyltransferase is an independent predictor of shortened progression free survival in patients with low-grade diffuse astrocytomas.

Autori: Komine C., Watanabe T., Katayama Y., Yoshino A., Yokoyama T., Fukushima T.

Data di Pubblicazione: 2003-5-15

Abstract: The O6-methylguanine-DNA methyltransferase (MGMT) plays a major role in repairing DNA damage from alkylating agents. In several human neoplasms including low-grade diffuse astrocytomas, promoter hypermethylation of MGMT has been shown to correlate with an increased frequency of p53 mutation. In the present study, we analyzed MGMT promoter methylation by the methylation-specific PCR in 49 newly diagnosed WHO grade II astrocytomas and evaluated its clinical usefulness. MGMT promoter methylation was found in 21 (43%) of the 49 tumors. A tight correlation existed between MGMT methylation and p53 protein accumulation ( $P=0.0424$ ). The presence of MGMT methylation was significantly associated with a shorter progression free survival (PFS) on both univariate analysis ( $P=0.0014$ ) and multivariate analysis ( $P=0.0081$ ). It was a more powerful determinant of the PFS than age, sex, performance status, proliferative activity, or p53 expression, and was independent of the extent of surgery. In terms of the overall survival, MGMT methylation demonstrated a prognostic utility in the univariate analysis but not in the multivariate analysis. The present findings indicate that aberrant methylation of the MGMT promoter independently augurs for an unfavorable clinical course in patients with low-grade diffuse astrocytomas. Since the presence of MGMT methylation is expected to predict an increased sensitivity to alkylating chemotherapeutic agents, earlier chemotherapy could serve to improve an unfavorable natural history in tumors with MGMT methylation.

Journal Title: Brain pathology (Zurich, Switzerland)

PUBMED ID: 12675529

DOI: doi.org/10.1023/a:1022644031905

Titolo: Quantifying efficacy of chemotherapy of brain tumors with homogeneous and heterogeneous drug delivery.

Autori: Swanson KR., Alvord EC., Murray JD.

Data di Pubblicazione: 2003-4-5



Abstract: Gliomas are diffuse and invasive brain tumors with the nefarious ability to evade even seemingly draconian treatment measures. Here we introduce a simple mathematical model for drug delivery of chemotherapeutic agents to treat such a tumor. The model predicts that heterogeneity in drug delivery related to variability in vascular density throughout the brain results in an apparent tumor reduction based on imaging studies despite continual spread beyond the resolution of the imaging modality. We discuss a clinical example for which the model-predicted scenario is relevant. The analysis and results suggest an explanation for the clinical problem of the long-standing confounding observation of shrinkage of the lesion in certain areas of the brain with continued growth in other areas.

Journal Title: Acta biotheoretica

PUBMED ID: 12654425

DOI: doi.org/10.1016/s0360-3016(02)04391-2

Titolo: A phase I trial of etanidazole and hyperfractionated radiotherapy in children with diffuse brainstem glioma.

Autori: Marcus KJ., Dutton SC., Barnes P., Coleman CN., Pomeroy SL., Goumnerova L., Billett AL., Kieran M., Tarbell NJ.

Data di Pubblicazione: 2003-3-26

Abstract: The MTD of etanidazole in children receiving HRT for brainstem glioma is 42g/m<sup>2</sup>, with cutaneous rash as the dose-limiting toxicity. This is in contrast to the adult experience, which demonstrates a 24% lower MTD of 34 g/m<sup>2</sup> limited by peripheral neuropathy.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 12587796

DOI: doi.org/10.1023/a:1021204616334

Titolo: Clinicopathological study of seven cases of symptomatic supratentorial subependymoma.

Autori: Im SH., Paek SH., Choi YL., Chi JG., Kim DG., Jung HW., Cho BK.

Data di Pubblicazione: 2003-2-18

Abstract: Subependymomas are rare, slow-growing tumors, the majority of which are found incidentally at postmortem examination. The authors retrospectively analyzed seven cases of symptomatic supratentorial subependymomas. Five were females and two were males, ranging in age at operation of 6-50 years (median 45). The follow-up period ranged from 1.5 to 8.3 years. Tumors were intraventricularly located as a lobulated mass with cystic changes: four in the frontal horn, two in the trigone, and one in the third ventricle. Moderate to marked enhancement was noted in two tumors of the trigone and in one tumor of the frontal horn on both CT scan and MR imaging. MR spectroscopy of a recurrent subependymoma demonstrated a higher Cho/Cr ratio of 2.66, compared with a Cho/Cr ratio (0.48) of a non-recurrent subependymoma. Angiography, which was performed in four patients, revealed no staining in two and delayed modest staining in two. Radiosurgery was performed in two patients but was ineffective. Five patients with gross total tumor resection showed no evidence of tumor recurrence to the last follow-up. The two subtotally resected trigonal tumors progressed two years after operation. No histological difference except MIB-1 index was noted between recurrent and non-recurrent cases. In conclusion, we suggest that subependymoma could show progressive biological behavior, especially in cases of markedly enhancing, irregularly contoured, large tumors located in the trigone. For symptomatic supratentorial subependymomas, gross total resection is the treatment of choice and radiation has little effect on tumor control.

Journal Title: Journal of neuro-oncology

PUBMED ID: 12586801

DOI: doi.org/10.1200/JCO.2003.01.009

Titolo: Phase II trial of temozolomide in patients with progressive low-grade glioma.

Autori: Quinn JA., Reardon DA., Friedman AH., Rich JN., Sampson JH., Provenzale JM., McLendon RE., Gururangan S., Bigner DD., Herndon JE., Avgeropoulos N., Finlay J., Tourt-Uhlig S., Affronti ML., Evans B., Stafford-Fox V., Zaknoen S., Friedman HS.

Data di Pubblicazione: 2003-2-15

Abstract: Initial results indicate that Temodar may be active in the treatment of low-grade glioma, and thus, further evaluation of this agent in the treatment of these tumors is warranted.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 12510774

DOI: doi.org/10.1023/a:1021184400053

Titolo: Results of three-dimensional stereotactically-guided radiotherapy in recurrent medulloblastoma.

Autori: Milker-Zabel S., Zabel A., Thilmann C., Zuna I., Hoess A., Wannenmacher M., Debus J.

Data di Pubblicazione: 2003-1-4

Abstract: SRT is effective and safe in the treatment of recurrent medulloblastoma to improve local control without evident side effects. The main problem remains the control of subclinical cranio-spinal dissemination.

Journal Title: Journal of neuro-oncology

PUBMED ID: 12449727

DOI: doi.org/10.1081/cnv-120005910

Titolo: CI-980 for the treatment of recurrent or progressive malignant gliomas: national central nervous system consortium phase I-II evaluation of CI-980.

Autori: Kunschner LJ., Fine H., Hess K., Jaeckle K., Kyritsis AP., Yung WK.

Data di Pubblicazione: 2002-11-27

Abstract: These results fail to demonstrate the significant activity of CI-980 against recurrent glioma.

Journal Title: Cancer investigation

PUBMED ID: 12434281

DOI: doi.org/10.1038/sj.bjc.6600552

Titolo: Treatment of paediatric pontine glioma with oral trophosphamide and etoposide.

Autori: Wolff JE., Westphal S., Mölenkamp G., Gnekow A., Warmuth-Metz M., Rating D., Kuehl J.

Data di Pubblicazione: 2002-11-16

Abstract: To evaluate the overall survival of paediatric patients with pontine gliomas treated with oral trophosphamide and etoposide. Patients between 3 and 17 years of age with either typical diffuse pontine glioma on MRI or histologically proven anaplastic astrocytoma/glioblastoma multiforme located in the pons, were eligible. Treatment consisted of oral trophosphamide 100 mg x m(-2) x day(-1) combined with oral etoposide at 25 mg x m(-2) x day(-1) starting simultaneously with conventional radiation. Twenty patients were enrolled (median age 6 years, male : female=9 : 11). Surgical procedures included: no surgery: five, open biopsy: three, stereotactic biopsy: six, partial resection: three, and sub-total resection: three. Histological diagnoses included pilocytic astrocytoma: one, astrocytoma with no other specification: three, anaplastic astrocytoma: three, glioblastoma multiforme: eight, no histology: five. The most frequent side effects were haematologic and gastrointe

stinal. There was no toxic death. The response to combined treatment in 12 evaluable patients was: complete response: 0, partial response: three, stable disease: four, and progressive disease: five. All tumours progressed locally and all patients died. The overall median survival was 8 months. The overall survival rates at 1 and 4 years were: 0.4 and 0.05 respectively. This was not different from a control group of patients documented in the same population. Oral trophosphamide in combination with etoposide did not improve survival of pontine glioma patients. The treatment was well tolerated and should be evaluated for more chemoresponsive paediatric malignancies.  
Journal Title: British journal of cancer

PUBMED ID: 12397464

DOI: doi.org/10.1007/s00259-002-0896-0

Titolo: Detection of tumour progression in the follow-up of irradiated low-grade astrocytomas: comparison of 3-[123I]iodo-alpha-methyl- L-tyrosine and 99mTc-MIBI SPET.

Autori: Henze M., Mohammed A., Schlemmer H., Herfarth KK., Mier W., Eisenhut M., Debus J., Haberkorn U.

Data di Pubblicazione: 2002-10-25

Abstract: Conventional MRI often fails to distinguish between progressive tumour and radiation injury, because both appear as mass lesions with unspecific Gd-DTPA enhancement. Furthermore, the sensitivity of FDG PET for the evaluation of malignant lesions in the brain is limited owing to high cortical uptake. The aim of this study was to assess the potential of alternative SPET tracers in the same group of patients. 35.2+/-20.1 months after stereotactic radiotherapy (59.3+/-4.2 Gy) of low-grade astrocytomas (median WHO II), 16 patients, presenting 25 Gd-DTPA-enhancing lesions on MRI, were examined by SPET. Lesions were classified as progressive tumour (PT, n=17) or non-PT (nPT, n=8) based on prospective follow-up (clinical examination, MRI, proton-MR spectroscopy) for 25.6+/-6.7 months after SPET. SPET scans were performed 15 and 60 min after injection of 694+/-67 MBq hexakis(2-methoxyisobutylisonitrile) (99m)Tc(I) (MIBI). 3-[(123)I]iodo-alpha-methyl- L-tyrosine (IMT) SPET was acquired 15 min after injection of 291+/-58 MBq IMT. Lesion-to-normal tissue ratios (l/n) for IMT (l/n(IMT)) and MIBI (l/n(MIBI)) were calculated using a reference region mirrored to the contralateral hemisphere. Using IMT, significantly higher ratios (P<0.001) were found in PT (1.7+/-0.4) than in nPT (1.1+/-0.1). For MIBI, there was no statistically significant difference (P=0.206) between PT (3.7+/-2.8) and nPT (1.8+/-1.8). Sensitivities for MIBI and IMT were 53% and 94%, and specificities 75% and 100%, respectively. Positive predictive values for MIBI and IMT respectively reached 80% and 100%, and negative predictive values were 46% and 90%. In conclusion, in contrast to MIBI, IMT showed almost no overlap between the PT and the nPT group. The sensitivity, specificity and predictive values of IMT SPET were obviously higher than those of MIBI SPET. IMT is considered to be a useful tracer for differentiating PT from nPT in the follow-up of irradiated low-grade astrocytomas.  
Journal Title: European journal of nuclear medicine and molecular imaging

PUBMED ID: 12356355

DOI: doi.org/10.1093/neuonc/4.4.253

Titolo: Leptomeningeal dissemination in children with progressive low-grade neuroepithelial tumors.

Autori: Hukin J., Siffert J., Velasquez L., Zagzag D., Allen J.

Data di Pubblicazione: 2002-10-3

Abstract: Our purpose is to describe the incidence and clinical features of leptomeningeal dissemination (LM) in children with progressive low-grade neuroepithelial tumor (LGN). We have continuously tracked all patients with primary CNS tumors since 1986. Satisfactorily followed data were obtained on 427 of the 588 patients with localized LGN at diagnosis between 1986 and 1998,

177 (42%) of whom developed progressive or recurrent disease. LM was identified in 13/177 (7%). The median age at initial diagnosis was 5 years and at LM diagnosis was 8.5 years. The primary tumor sites were diencephalon (6), brainstem (3), cerebellum (2), cerebrum (1), and spinal cord (1). The histologies were pilocytic astrocytoma (4), ganglioglioma (4), fibrillary astrocytoma (3), mixed glioma (1), and glioneurofibroma (1). Management included chemotherapy (2) or radiotherapy (3) or both (7); 1 patient received only radical resections of symptomatic lesions. The 5-year progression-free survival rates for patients with localized versus LM disease at recurrence were 22% (95% confidence interval [CI], 13%-25%) versus 15% (95% CI, 0.1%-36%), respectively (P = 0.28). The 5- and 10-year overall survival rates for patients with localized disease versus LM were 87% (95% CI, 82%-92%) and 83% (95% CI, 77%-89%) versus 68% (95% CI, 39%-91%) and 68% (95% CI, 39%-91%), respectively (P = 0.05). The 7% incidence of LM is a low estimate because patients were not routinely staged at recurrence. Tumors arising from the diencephalon appeared to predispose to LM; no other predisposing features were identified. We strongly urge that for optimum treatment planning all patients with recurrent LGN be staged with an enhanced spine and brain MRI before adjuvant therapy is initiated. The good survival of patients with LGN and LM reflects a more indolent disease than malignant CNS tumors with LM.

Journal Title: Neuro-oncology

PUBMED ID: 12209758

DOI: doi.org/10.1002/cncr.10710

Titolo: Evaluation of the efficiency of chemotherapy in in vivo orthotopic models of human glioma cells with and without 1p19q deletions and in C6 rat orthotopic allografts serving for the evaluation of surgery combined with chemotherapy.

Autori: Branle F., Lefranc F., Camby I., Jeuken J., Geurts-Moespot A., Sprenger S., Sweep F., Kiss R., Salmon I.

Data di Pubblicazione: 2002-9-5

Abstract: The in vivo models of gliomas of the central nervous system developed in the current work best mimicked clinical reality. They can be used either to identify new therapies against human gliomas or to optimize existing therapies.

Journal Title: Cancer

PUBMED ID: 12209682

DOI: doi.org/10.1002/cncr.10826

Titolo: Salvage chemotherapy for recurrent spinal cord ependymoma.

Autori: Chamberlain MC.

Data di Pubblicazione: 2002-9-5

Abstract: Chronic oral etoposide appears to be well tolerated, has modest toxicity, and had apparent activity in the small cohort of adults in the current study with surgically and medically refractory, recurrent, intradural intramedullary SCE.

Journal Title: Cancer

PUBMED ID: 12174942

DOI: Mancante

Titolo: Treatment of recurrent malignant supratentorial astrocytomas with carboplatin and etoposide combined with recombinant mutant human tumor necrosis factor-alpha.

Autori: Yamamoto M., Oshiro S., Tsugu H., Hirakawa K., Ikeda K., Soma G., Fukushima T.

Data di Pubblicazione: 2002-8-15

Abstract: These results suggest that combined therapy with carboplatin, etoposide and recombinant mutant TNF-alpha in this patient population seems to be safe and acceptable and may benefit those with recurrent anaplastic astrocytomas. These intriguing clinical observations warrant a properly stratified randomized trial to determine whether this approach can provide therapeutic benefits and improve survival.

Journal Title: Anticancer research

PUBMED ID: 12160138

DOI: doi.org/10.1023/a:1015853200090

Titolo: Hypersensitivity reactions to carboplatin in children.

Autori: Lazzareschi I., Ruggiero A., Riccardi R., Attinà G., Colosimo C., La sorella A.

Data di Pubblicazione: 2002-8-6

Abstract: Hypersensitivity reactions to carboplatin are rare but sometimes life-threatening events may occur requiring discontinuation of treatment. In our study, we describe clinical features and diagnostic procedures of carboplatin-associated reactions in children affected by low-grade astrocytoma and treated with multiple courses of carboplatin. In 6 out of 29 children, we reported allergic events. We also report a desensitization protocol for carboplatin administration, which allowed the patients to receive effective treatment without adverse reactions.

Journal Title: Journal of neuro-oncology

PUBMED ID: 12125988

DOI: doi.org/10.1023/a:1015788814667

Titolo: Temozolomide as second-line chemotherapy for relapsed gliomas.

Autori: Trent S., Kong A., Short SC., Traish D., Ashley S., Dowe A., Hines F., Brada M.

Data di Pubblicazione: 2002-7-20

Abstract: In the small cohort of patients with recurrent malignant glioma who failed PCV chemotherapy temozolomide demonstrated limited activity as second-line treatment although this remains within the confidence intervals of response seen in patients with glioblastoma.

Journal Title: Journal of neuro-oncology

PUBMED ID: 12089224

DOI: doi.org/10.1200/JCO.2002.12.008

Titolo: Phase II study of carboplatin in children with progressive low-grade gliomas.

Autori: Gururangan S., Cavazos CM., Ashley D., Herndon JE., Bruggers CS., Moghrabi A., Scarcella DL., Watral M., Tourt-Uhlig S., Reardon D., Friedman HS.

Data di Pubblicazione: 2002-6-29

Abstract: Carboplatin, in the schedule used in this study, produced disease stabilization or improvement in a majority of children with progressive low-grade glioma, with manageable toxicity. Improved treatment strategies are particularly required for patients with diencephalic tumors.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 12057097

DOI: doi.org/10.1007/s11864-001-0073-x

Titolo: Neoplastic meningitis.

Autori: Kim L., Glantz MJ.

Data di Pubblicazione: 2002-6-12

**Abstract:** Neoplastic meningitis is recognized clinically in 4% to 7% of patients with extraneural cancer, but it remains dramatically under-diagnosed. The frequency of neoplastic meningitis is increasing because of heightened clinical suspicion, improved neuroimaging techniques, and longer survival in patients with extraneural cancer. Longer survival allows residual tumor cells within central nervous system sanctuary sites time to become symptomatic. Affected patients may present with cerebral, cranial nerve, or spinal signs and symptoms, depending on the specific sites of central nervous system (CNS) involvement. Magnetic Resonance Imaging (MRI) seems to be sensitive for detecting metastatic deposits along the neuraxis. However, metastases at a microscopic level are below the resolution of MRI scanning. As a result, the standard diagnostic test for neoplastic meningitis remains the cytologic identification of malignant cells in cerebrospinal fluid (CSF). Although CSF cytology is useful, malignant cells are not detected in as many as one third of patients who have compelling clinical or radiographic evidence of neoplastic meningitis. Novel assays are being tested that may enhance the early identification of malignant cells in CSF. Currently, the diagnosis occurs generally after the onset of neurologic manifestations and heralds a rapidly fatal course for most patients. By the time symptoms appear, most tumors have disseminated widely within the CNS, due to cortical irritation, compression of nervous system structures, or obstruction of CSF flow. At this stage surgery, cranial irradiation, and chemotherapy are rarely, if ever, curative. The goals of treatment are to improve or to stabilize the neurologic status of patients and to prolong survival. A major problem in treating neoplastic meningitis is that the entire neuraxis must be treated. If only symptomatic areas are treated, reseeding of the neuraxis with tumor cells will occur. Therefore, intrathecal chemotherapy remains a mainstay of therapy. Currently, four therapeutic agents are available for intrathecal treatment: methotrexate, ara-C, sustained-release ara-C (DepoCyt; Chiron Therapeutics, San Francisco, CA), and thiotepea. Unfortunately, intrathecal chemotherapy does not treat bulky disease in the subarachnoid space, and often is slow to stabilize progressive neurologic deficits. For these reasons, radiation therapy to sites of symptomatic disease and sites of bulky disease on imaging studies is recommended. High dose intravenous methotrexate may be as effective as intrathecal methotrexate. Alternative approaches (which offer less toxicity, enhanced therapeutic effect, and prolonged survival) are being investigated.

**Journal Title:** Current treatment options in oncology

PUBMED ID: 11980998

DOI: doi.org/10.1200/JCO.2002.09.084

**Titolo:** Phase II trial of carmustine plus O(6)-benzylguanine for patients with nitrosourea-resistant recurrent or progressive malignant glioma.

**Autori:** Quinn JA., Pluda J., Dolan ME., Delaney S., Kaplan R., Rich JN., Friedman AH., Reardon DA., Sampson JH., Colvin OM., Haglund MM., Pegg AE., Moschel RC., McLendon RE., Provenzale JM., Gururangan S., Tourt-Uhlig S., Herndon JE., Bigner DD., Friedman HS.

**Data di Pubblicazione:** 2002-5-1

**Abstract:** These results indicate that O(6)-BG plus BCNU at the dose schedule used in this trial is unsuccessful in producing tumor regression in patients with nitrosourea-resistant malignant glioma, although stable disease was seen in five patients for 6, 12, 12, and 18 weeks. Future use of this approach will require strategies to minimize dose-limiting toxicity of BCNU such as regional delivery or hematopoietic stem-cell protection.

**Journal Title:** Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 11949830

DOI: doi.org/10.1023/a:1014498225405

Titolo: Intra-arterial carboplatin and intravenous etoposide for the treatment of recurrent and progressive non-GBM gliomas.

Autori: Newton HB., Slivka MA., Stevens CL., Bourekas EC., Christoforidis GA., Baujan MA., Chakeres DW.

Data di Pubblicazione: 2002-4-13

Abstract: Recurrent and progressive non-GBM gliomas are a diverse group of brain tumors that often respond poorly to adjuvant chemotherapy treatment. Regional intra-arterial (IA) administration of chemotherapy may result in increased tumor uptake of drug, with improvement in response rates and time to progression (TTP). Twenty-five patients with recurrent or progressive non-GBM gliomas were treated with IA carboplatin (200 mg/m<sup>2</sup>/d) and intravenous (IV) etoposide (100 mg/m<sup>2</sup>/d) for 2 days every 4 weeks. Patients ranged in age from 22 to 68 years (mean 37.8). All but one patient had received standard irradiation, and eight patients had attempted prior chemotherapy. Five of 25 patients had objective responses (20%), while another 15 patients had stable disease (60%), receiving a total of 318 IA treatment procedures. There was one complete response (4.0%), three partial responses (12.0%), one minor response (4.0%), 15 stable diseases (60.0%), and five progressive diseases (20.0%). The median TTP was 24.2 weeks overall and 32 weeks in responders. Overall median survival was 34.2 weeks. Therapy was well tolerated, with mainly hematologic toxicity. Two patients had embolic complications. Although these are preliminary results, IA carboplatin and IV etoposide have modest activity against recurrent and progressive non-GBM gliomas and warrants further study.

Journal Title: Journal of neuro-oncology

PUBMED ID: 11916502

DOI: Mancante

Titolo: A phase II trial of thymidine and carboplatin for recurrent malignant glioma: a North American Brain Tumor Consortium Study.

Autori: Robins HI., Chang SM., Prados MD., Yung WK., Hess K., Schiff D., Greenberg H., Fink K., Nicolas K., Kuhn JG., Cloughesy T., Junck L., Mehta M.

Data di Pubblicazione: 2002-3-28

Abstract: This phase II study in recurrent high-grade glioma evaluated the response rate, toxicities, and time to treatment failure of high-dose carboplatin modulated by a 24-h infusion of thymidine (75 g/m<sup>2</sup>). The trial was based on preclinical data and a prior phase I study (J. Clin. Oncol. 17, 2922-2931, 1999); a phase II recurrent high-grade glioma study was initiated in July of 1998. Thymidine was given over 24 h; carboplatin was given over 20 min at hour 20 of the thymidine infusion. The starting dose of carboplatin had a value of 7 for the area under the curve (AUC), with allowance for dose escalation of 1 AUC unit per cycle if grade 2 toxicity was observed. Treatment cycles were repeated every 4 weeks. Accrual as of September 1999 was 45 patients [4 were unevaluable]: 76% with glioblastoma multiforme (GBM), 20% with anaplastic oligodendroglioma, 2% with mixed type, and 2% with anaplastic astrocytoma. Most patients had prior chemotherapy (78%). As observed in the earlier phase I study (in which carboplatin pharmacokinetics were unaltered by thymidine or antiepileptic medications), thymidine was myeloprotective, resulting in a minimal need for dose reduction for patients having a >2 grade toxicity (in only 4% of the courses of treatment). Of 101 total courses, the number of courses (at the AUCs) was 3 (5), 4 (6), 58 (7), 20 (8), 11 (9), and 5 (10). Grade 3 nonhematologic toxicities included headache (4%), altered consciousness (3%), fatigue (1%), and nausea (3%). Responses included 2 partial (1 oligodendroglioma, 1 GBM; 5%); 3 minor (1 anaplastic astrocytoma, 2 GBM; 7.3%); 6 stable disease (14.6%); and 30 progressive disease (73.2%). For GBM patients, median survival was 23 weeks (with a 95% confidence interval of 20 to 50 weeks), and progression-free survival was 8 weeks (with a 95% confidence interval of 7-16 weeks). These results in GBM were comparable to other phase II GBM trials and thus do not represent a therapeutic advance in the treatment of GBM. Taken collectively, however, results are consistent with co

ntinued investigation of thymidine in combination with chemotherapeutic agents for high-grade glioma and other malignant diseases. The significant myelo protection afforded by thymidine may have particular relevance to polychemotherapeutic regimens.

Journal Title: Neuro-oncology

PUBMED ID: 11914886

DOI: doi.org/10.1007/s00259-001-0717-x

Titolo: Local injection of the 90Y-labelled peptidic vector DOTATOC to control gliomas of WHO grades II and III: an extended pilot study.

Autori: Schumacher T., Hofer S., Eichhorn K., Wasner M., Zimmerer S., Freitag P., Probst A., Gratzl O., Reubi JC., Maecke R., Mueller-Brand J., Merlo A.

Data di Pubblicazione: 2002-3-27

Abstract: We have previously presented preliminary observations on targeting somatostatin receptor-positive malignant gliomas of all grades by local injection of the radiolabelled peptidic vector 90Y-DOTATOC. We now report on our more thorough clinical experience with this novel compound, focussing on low-grade and anaplastic gliomas. Small peptidic vectors have the potential to target invisible infiltrative disease within normal surrounding brain tissue, thereby opening a window of opportunity for early intervention. Five progressive gliomas of WHO grades II and III and five extensively debulked low-grade gliomas were treated with varying fractions of 90Y-DOTATOC. The vectors were locally injected into the resection cavity or into solid tumour. The activity per single injection ranged from 555 to 1,875 MBq, and the cumulative activity from 555 to 7,030 MBq, according to tumour volumes and eloquence of the affected brain area, yielding dose estimates from 76+/-15 to 312+/-62 Gy. Response was assessed by the clinical status, by steroid dependence and, every 4-6 months, by magnetic resonance imaging and fluorine-18 fluorodeoxyglucose positron emission tomography. In the five progressive gliomas, lasting responses were obtained for at least 13-45 months without the need for steroids. Radiopeptide brachytherapy had been the only modality applied to counter tumour progression. Interestingly, we observed the slow transformation of a solid, primarily inoperable anaplastic astrocytoma into a resectable multicystic lesion 2 years after radiopeptide brachytherapy. Based on these observations, we also assessed the feasibility of local radiotherapy following extensive debulking, which was well tolerated. Targeted beta-particle irradiation based on diffusible small peptidic vectors appears to be a promising modality for the treatment of malignant gliomas.

Journal Title: European journal of nuclear medicine and molecular imaging

PUBMED ID: 11902299

DOI: doi.org/10.1097/00043426-200112000-00004

Titolo: Visual improvement despite radiologically stable disease after treatment with carboplatin in children with progressive low-grade optic/thalamic gliomas.

Autori: Mitchell AE., Elder JE., Mackey DA., Waters KD., Ashley DM.

Data di Pubblicazione: 2002-3-21

Abstract: The results suggest that the clinical response of optic/thalamic gliomas to carboplatin, as measured by visual acuity and visual fields, may be better than predicted by radiologic assessment. These data suggest that a prospective clinical study is warranted of the role of carboplatin in children with progressive optic/thalamic gliomas and visual impairment.

Journal Title: Journal of pediatric hematology/oncology

PUBMED ID: 11870183

DOI: doi.org/10.1200/JCO.2002.20.5.1383



Titolo: Phase II trial of temozolomide plus the matrix metalloproteinase inhibitor, marimastat, in recurrent and progressive glioblastoma multiforme.

Autori: Groves MD., Puduvalli VK., Hess KR., Jaeckle KA., Peterson P., Yung WK., Levin VA.

Data di Pubblicazione: 2002-3-1

Abstract: The combination of TMZ and MRM resulted in a PFS at 6 months that exceeded the literature target by 29%. This drug combination met phase II study criteria; further study in recurrent patients with GBM might be warranted. Further study of therapy-induced joint pain is necessary.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 11846927

DOI: doi.org/10.1097/00006123-200112000-00002

Titolo: Age and radiation response in glioblastoma multiforme.

Autori: Barker FG., Chang SM., Larson DA., Sneed PK., Wara WM., Wilson CB., Prados MD.

Data di Pubblicazione: 2002-2-16

Abstract: Older GM patients are less likely to have good responses to postoperative external beam radiation therapy. Karnofsky Performance Scale score before radiation treatment and extent of surgical resection are additional predictors of radiographically assessed radiation response in GM.

Journal Title: Neurosurgery

PUBMED ID: 11804278

DOI: doi.org/10.1023/a:1012982303419

Titolo: Gliomatosis cerebri: post-mortem molecular and immunohistochemical analyses in a case treated with thalidomide.

Autori: Mawrin C., Aumann V., Kirches E., Schneider-Stock R., Scherlach C., Vogel S., Mittler U., Dietzmann K., Krause G., Weis S.

Data di Pubblicazione: 2002-1-24

Abstract: Gliomatosis cerebri (GC) is a rare tumor of the central nervous system (CNS) characterized by widespread diffuse infiltration of the brain and spinal cord by neoplastic glial cells. We report the case of a 17-year-old boy with a bioptically diagnosed fibrillary astrocytoma. The administration of thalidomide, which was suggested to be beneficial in the treatment of human cancers, had no substantial clinical effect on our patient. Autopsy studies revealed a diffuse infiltration of the frontal and temporal lobes of the right hemisphere, brainstem, and the leptomeninges covering the whole spinal cord by an astrocytic tumor, which showed features both of low-grade astrocytoma and glioblastoma multiforme. No mutations in the p53 and PTEN tumor suppressor genes were found; immunoreactivities for p53, PTEN, and EGFR could not be detected.

Journal Title: Journal of neuro-oncology

PUBMED ID: 11772431

DOI: doi.org/10.1093/neuonc/4.1.39

Titolo: A phase II study of extended low-dose temozolomide in recurrent malignant gliomas.

Autori: Khan RB., Raizer JJ., Malkin MG., Bazylewicz KA., Abrey LE.

Data di Pubblicazione: 2002-1-5

Abstract: Temozolomide is an effective agent in the treatment of recurrent malignant gliomas. The standard dosage is 150-200 mg/m<sup>2</sup> per day for 5 days in a 28-day cycle. A prior phase I study established a chronic daily temozolomide dose that significantly increased the total dose administered and suggested a superior response rate. In a prospective phase II trial, we treated 35 patients with recurrent malignant gliomas with temozolomide 75 mg/m<sup>2</sup> per day

for 42 consecutive days in a 70-day cycle. Median age was 55 years (range, 27-73 years) and median Karnofsky performance score was 70 (range, 60-90). Twenty-eight (79%) patients had glioblastoma multiforme, 3 (9%) anaplastic astrocytoma, 2 (6%) anaplastic oligodendroglioma, and 2 (6%) anaplastic oligoastrocytoma. All but one had prior radiotherapy, and 27 had prior chemotherapy. There were 2 partial (anaplastic astrocytoma) and 3 minor (glioblastoma multiforme) radiographic responses; 17 patients had progressive disease at the end of the first cycle. In 55 cycles of temozolomide, there were 8 episodes of asymptomatic drug-related grade 3 toxicity: 6 lymphopenia, 1 neutropenia, and 1 thrombocytopenia. Median progression-free survival and overall survival were 2.5 and 8.7 months (2.3 and 7.7 months in glioblastoma multiforme patients). At 6 months, progression-free survival and overall survival rates were 27% and 67% (19% and 60% in glioblastoma multiforme). Quality of life scores did not change significantly during treatment. We conclude that the extended low-dose schedule of temozolomide is well tolerated in heavily pretreated patients; however, our results do not support an improved rate of response or survival.

Journal Title: Neuro-oncology

PUBMED ID: 11694768

DOI: doi.org/10.1159/000055122

Titolo: Therapeutic anti-angiogenesis for malignant brain tumors.

Autori: Kirsch M., Santarius T., Black PM., Schackert G.

Data di Pubblicazione: 2001-11-6

Abstract: Malignant brain tumors, especially malignant gliomas, have a poor prognosis, a fact which has remained unchanged over the last decades despite the employment of multimodal therapeutic approaches. Malignant gliomas are among the most vascularized tumors known and the amount of vascularization has been correlated to their prognosis. Since tumor growth is dependent on concomitant vascularization, recent experimental studies have focused on the use of anti-angiogenic molecules as a novel strategy in brain tumor therapy. Angiogenesis inhibitors target at proliferating endothelial cells and suppress the formation of a sufficient vascular bed. Inhibitors such as TNP-470, suramin and angiostatin have shown their therapeutic potential in experimental studies. In a clinical setting, they could be applied for the treatment of multiple tumors or postsurgically as an adjuvant therapy to prevent recurrence. This article discusses presently available anti-angiogenic agents, emphasizing on substances already in clinical trials.

Journal Title: Onkologie

PUBMED ID: 11685523

DOI: doi.org/10.1007/s003810100479

Titolo: Cerebellar astrocytomas: a 24-year experience.

Autori: Viano JC., Herrera EJ., Suárez JC.

Data di Pubblicazione: 2001-10-31

Abstract: The most frequent complication was increased ataxia. The mortality rate was 8.5%.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 11584894

DOI: doi.org/10.1093/neuonc/3.4.246

Titolo: Phase I study of Gliadel wafers plus temozolomide in adults with recurrent supratentorial high-grade gliomas.

Autori: Gururangan S., Cokgor L., Rich JN., Edwards S., Affronti ML., Quinn JA., Herndon JE., Provenzale JM., McLendon RE., Tourt-Uhlig S., Sampson JH., Stafford-Fox V., Zaknoen S., Early M., Friedman AH., Friedman HS.

Data di Pubblicazione: 2001-10-5

Abstract: Both Gliadel wafers [1,3-bis(2-chloroethyl)-1-nitrosourea] and temozolomide (TEMO) have been shown in independent studies to prolong survival of patients with recurrent malignant glioma following surgery and radiotherapy. On the basis of preclinical evidence of synergism between Gliadel wafers and TEMO, a phase I study was designed to evaluate the toxicity of combining these 2 agents in the treatment of patients with recurrent supratentorial malignant glioma. All patients had surgical resection of the tumor at relapse, and up to 8 Gliadel (3.85%) wafers were placed in the surgical cavity following resection. Two weeks after surgery, TEMO was given orally daily for 5 days. Cohorts of 3 patients received TEMO at daily doses of 100 mg/m<sup>2</sup>, 150 mg/m<sup>2</sup>, and 200 mg/m<sup>2</sup>, respectively. Patients were assessed for toxicity 4 weeks after start of the first course of TEMO. Contrast-enhanced MRI of the brain was used to assess tumor response after the first cycle of TEMO. Patients with stable disease or response after the first cycle of TEMO were allowed to continue treatment at the same dose every 4 weeks for 12 cycles or until disease progression or unacceptable toxicity. Ten patients with a median age of 47 years (range, 22-66 years) were enrolled in this study. There were 7 patients with glioblastoma multiforme and 3 patients with anaplastic astrocytoma. Three patients were treated with TEMO at the first dose level of 100 mg/m<sup>2</sup>, 4 at the second dose level of 150 mg/m<sup>2</sup>, and 3 at the third dose level of 200 mg/m<sup>2</sup>. The 10 patients received a median of 3 cycles (range, 1-12 cycles) of TEMO following placement of Gliadel wafers. The treatment was well tolerated, with only 1 patient suffering grade III thrombocytopenia at the highest dose level. Two patients at each dose level had no evidence of disease progression after treatment. Four patients suffered progressive disease on the study. Our study demonstrates that TEMO can be given safely after placement of Gliadel (3.85%) wafers. The recommended dosage for TEMO for a phase II study of this combination is 200 mg/m<sup>2</sup> per day for 5 days.

Journal Title: Neuro-oncology

PUBMED ID: 11485231

DOI: doi.org/10.1007/pl00012393

Titolo: Intracerebral ganglioglioma: clinical and radiological study of eleven surgically treated cases with follow-up.

Autori: Ildan F., Tuna M., Göçer İA., Erman T., Cetinalp E.

Data di Pubblicazione: 2001-8-4

Abstract: We conclude that ganglioglioma is a distinct histological phenomenon with mildly predictable clinical symptoms (seizures), mildly characteristic radiological features, and long-term survival after surgical resection without the need of adjuvant treatment such as radiotherapy.

Journal Title: Neurosurgical review

PUBMED ID: 11463801

DOI: doi.org/10.1093/jjco/hye059

Titolo: Radiotherapy combined with nimustine hydrochloride and etoposide for malignant gliomas: results of a pilot study.

Autori: Tanaka M., Shibui S., Nomura K., Nakanishi Y.

Data di Pubblicazione: 2001-7-21

Abstract: RT with ACNU and etoposide are feasible and well tolerated and the treatment results were comparable to the best results reported in the literature.

Journal Title: Japanese journal of clinical oncology

PUBMED ID: 11432894

DOI: doi.org/10.1200/JCO.2001.19.13.3260

Titolo: Toxicity, efficacy, and pharmacology of suramin in adults with recurrent high-grade gliomas.

Autori: Grossman SA., Phuphanich S., Lesser G., Rozental J., Grochow LB., Fisher J., Piantadosi S., Piantadosi S.

Data di Pubblicazione: 2001-7-4

Abstract: This study demonstrates that suramin is well tolerated by patients with recurrent high-grade gliomas and may have efficacy in this disease. Its pharmacology seems unaffected by anticonvulsants. As a result of this data, suramin and radiation are now being administered concurrently to patients with newly diagnosed glioblastoma multiforme, with survival as the primary outcome.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 11430722

DOI: Mancante

Titolo: Microcephalus, medulloblastoma and excessive toxicity from chemotherapy: an unusual presentation of Fanconi anaemia.

Autori: Ruud E., Wesenberg F.

Data di Pubblicazione: 2001-6-30

Abstract: Fanconi anaemia must always be suspected in patients who experience excessive toxicity from chemotherapy regardless of the type of malignancy and congenital malformations.

Journal Title: Acta paediatrica (Oslo, Norway : 1992)

PUBMED ID: 11429220

DOI: doi.org/10.1016/s0360-3016(01)01518-8

Titolo: Radiosurgery in the management of pediatric brain tumors.

Autori: Hodgson DC., Goumnerova LC., Loeffler JS., Dutton S., Black PM., Alexander E., Xu R., Kooy H., Silver B., Tarbell NJ.

Data di Pubblicazione: 2001-6-29

Abstract: SRS can be given safely to selected children with brain tumors. SRS appears to reduce the proportion of first failures occurring locally and is associated with better outcome when given as a part of initial management. Some patients with unresectable relapsed disease can be salvaged with SRS. SRS to multiple lesions does not appear to be curative. Serious neurologic symptoms requiring reoperation is infrequently caused by radionecrosis alone.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 11398944

DOI: doi.org/10.1007/s003810000402

Titolo: Clinical aspects and prognosis of ependymoma in infants and children. A single institution experience.

Autori: Humpl T., Neuser H., Brühl K., Bartels U., Schwarz M., Gutjahr P.

Data di Pubblicazione: 2001-6-12

Abstract: Thirty-two patients (22 boys and 10 girls) with a histologically confirmed diagnosis of ependymoma were treated between 1972 and 1999. A total macroscopic resection was achieved in 16 of these patients, whereas 15 resections were classified by the surgeon as subtotal. In 1 patient a ventriculostomy was created as part of a palliative strategy. All children over 3 years old were treated with postoperative radiotherapy. Chemotherapy consisted of procarbazine, ifosfamide, etoposide, methotrexate, cisplatin and cytosine arabinoside. There was 1 perioperative death. Twenty children developed a relapse of disease within 2 months to 13 years and 1 month after the initial therapy. A maximal number of five recurrences were seen in 1 patient. The value of adjuvant chemotherapy on the prognosis of children with ependymoma seems

to be limited. With regard to the poor outcome, the advisability of further treatment after multiple recurrences is debatable.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 11394532

DOI: doi.org/10.1089/02724570152057634

Titolo: Phase I clinical evaluation of a neutralizing monoclonal antibody against epidermal growth factor receptor in advanced brain tumor patients: preliminary study.

Autori: Crombet T., Torres O., Rodríguez V., Menéndez A., Stevenson A., Ramos M., Torres F., Figueredo R., Veitia I., Iznaga N., Pérez R., Lage A.

Data di Pubblicazione: 2001-6-8

Abstract: High levels of growth factors and their receptors have been demonstrated in human tumors. Gliomas and meningiomas are characterized by overexpression of epidermal growth factor receptor (EGF-R). Ior egf/r3, is a neutralizing murine monoclonal antibody (MAb) against EGF-R, and was generated at the Cuban Institute of Oncology. The antibody recognizes EGF-R with high affinity, inhibiting tyrosine kinase activation. A clinical trial was conducted in brain tumor patients to evaluate toxicity, immunogenicity, and clinical benefit of escalating doses of the antibody. Nine patients with histologically confirmed gliomas or meningiomas, who had active or recurrent disease after receiving conventional treatment, received four intravenous doses of ior egf/r3. Total dosages ranged from 160 to 480 mg. As inclusion criteria, radioimmunoscinigraphy with the same MAb labeled with 99mTechnetium (99mTc) was performed. Immune response against the murine antibody was also evaluated. After four doses of ior egf/r3 MAb, no significant toxicity was found, except in one patient who developed a grade 4 allergic adverse event. This reaction was probably related with previous sensitization to the same MAb and the development of human anti-mouse antibodies (HAMA) response. Despite no major objective antitumor responses, eight patients had stable disease on the 6-month evaluation, and two patients remain alive after four years of MAb therapy. Journal Title: Hybridoma

PUBMED ID: 11355088

DOI: Mancante

Titolo: Diagnosis and results of treatment with radiation therapy in gliomatosis cerebri patient: case report.

Autori: Sun LM., Lui CC., Huang SC., Lu K., Wang CJ.

Data di Pubblicazione: 2001-5-18

Abstract: Gliomatosis cerebri (GC) is a rare disease loosely defined as a diffusely infiltrating glioma involving extensive areas of the brain. The prognosis is poor and no definite treatment has proven effective for GC. Little information exists regarding the role of radiation therapy (RT) for GC, but some researchers have suggested that it is a good choice of treatment from their limited experience. In this report, we present a case with imaging and histological diagnosis of GC and demonstrate the treatment results of RT. The patient was a 39-year-old woman with progressive symptoms of dizziness, unsteady gait, headache, vomiting, and consciousness disturbance for 6 months. She received a series of radiographic examinations and surgical interventions for diagnosis. The definite diagnosis of GC was made by a combination of magnetic resonance imaging (MRI) findings and histological examinations. Forty Gray (Gy) of whole brain irradiation followed by 14 Gy reduced-field boosts were given to her. The MRI, following treatment, showed regressive changes, and clinical symptoms were slightly improved. The patient survived 19 months after the diagnosis, which is longer than the average survival time of patients without treatment.

Journal Title: Chang Gung medical journal

PUBMED ID: 11349883

DOI: doi.org/10.1023/a:1006441104260

Titolo: Intra-arterial cisplatin plus oral etoposide for the treatment of recurrent malignant glioma: a phase II study.

Autori: Ashby LS., Shapiro WR.

Data di Pubblicazione: 2001-5-15

Abstract: Twenty-five adults with recurrent malignant glioma were enrolled into a phase II clinical study. All patients had undergone surgical resection and had failed radiotherapy and first-line treatment with nitrosourea-based chemotherapy; five had failed second-line chemotherapy. Our objective was to test the efficacy of combining intra-arterially (i.a.) infused cisplatin and oral etoposide. Using conventional angiographic technique to access anterior/posterior cerebral circulation, cisplatin 60 mg/m<sup>2</sup> was administered by i.a. infusion on day 1 of treatment. Oral etoposide 50 mg/m<sup>2</sup>/day was given days 1-21, with a 7 day rest interval between courses. Response to treatment was evaluated in 20 patients. Two patients with anaplastic astrocytoma had partial responses (PR) and six patients experienced stable disease (SD) for an overall response rate (PR +/- SD) of 40%. The median time to disease progression (MTP) following treatment for the responder subgroup was 18 weeks. The median survival time from treatment (MST) for the responders (n = 8) and non-responders (n = 12) was 56.5 weeks and 11 weeks, respectively. Combined i.a. cisplatin and oral etoposide was well-tolerated, but produced an objective response in only a minority of patients. Those considered responders (PR + SD) experienced significant survival advantage when compared to the non-responders. Nonetheless, i.a. delivery of chemotherapy is an expensive and technologically burdensome treatment for most patients to access, requiring proximity to a major center with neuro-oncological and neuroradiological clinical services. This is of special concern for patients suffering recurrent disease with progressive neurological symptoms at a time in their course when quality of life must be safeguarded and palliation of symptoms should be the therapeutic goal. Despite the efforts of previous investigators to use this combination of agents to treat recurrent malignant glioma, we cannot recommend the use of i.a. chemotherapy for salvage treatment of this disease.

Journal Title: Journal of neuro-oncology

PUBMED ID: 11349879

DOI: doi.org/10.1023/a:1006414804835

Titolo: Thalidomide as an anti-angiogenic agent in relapsed gliomas.

Autori: Short SC., Traish D., Dowe A., Hines F., Gore M., Brada M.

Data di Pubblicazione: 2001-5-15

Abstract: The efficacy of thalidomide in terms of response in recurrent gliomas is low, with a partial response rate of only 6%. Future studies should investigate thalidomide in combination with other agents and at an earlier stage of disease. Methods to assess anti-angiogenic properties such as changes in tumour vasculature could be employed as initial surrogate end-points in the investigation of efficacy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 11337321

DOI: Mancante

Titolo: Combined intraarterial carboplatin, intraarterial etoposide phosphate, and IV Cytosan chemotherapy for progressive optic-hypothalamic gliomas in young children.

Autori: Osztie E., Várallyay P., Doolittle ND., Lacy C., Jones G., Nickolson HS., Neuwelt EA.

Data di Pubblicazione: 2001-5-5

Abstract: These results suggest that this modality of chemotherapy (administered after failure of systemic [ie, IV] chemotherapy), of progressive optic-hypothalamic astrocytomas in young children may be an effective treatment prior to radiotherapy.

Journal Title: AJNR. American journal of neuroradiology

PUBMED ID: 11265230

DOI: doi.org/10.1093/neuonc/2.4.213

Titolo: Carboplatin is effective therapy for young children with progressive optic pathway tumors: a Pediatric Oncology Group phase II study.

Autori: Mahoney DH., Cohen ME., Friedman HS., Kepner JL., Gerner L., Langston JW., James HE., Duffner PK., Kun LE.

Data di Pubblicazione: 2001-3-27

Abstract: The Pediatric Oncology Group conducted a phase II study to evaluate the activity of carboplatin in children 5 years or younger with progressive optic pathway tumors (OPTs). Of the 51 patients accrued to this study, 1 was not eligible because the child was older than 6 years. Fifty patients were eligible and had either neuro-imaging or symptomatic evidence of progressive OPTs. Twenty-one of 50 had evidence of neurofibromatosis type I (NF-1). Therapy consisted of carboplatin 560 mg/m<sup>2</sup> at 4-week intervals. Patients with stable disease or better after two courses were continued on therapy for 18 months or until progressive disease. Of the 50 eligible children, 39 had stable disease or better, and 34 completed the 18-month therapy. Our data are sufficient to conclude that the proportion of objective responses (complete, partial, or minor response or stable disease) exceeded 30% ( $P < 0.00001$ ), and the approximate 95% confidence interval estimate of the objective response rate was 0.665 to 0.895. Twenty-one patients went off protocol because of progressive disease. Fifteen patients progressed during the 18-month therapy, and 6 patients progressed after completing therapy. Six children died with progressive disease. Major toxicities were neutropenia and thrombocytopenia, and 3 children experienced allergic reactions. Carboplatin is active and safe for the treatment of young children with progressive OPTs. The addition of other potentially active drugs may further increase the event-free survival for these children.

Journal Title: Neuro-oncology

PUBMED ID: 11212902

DOI: doi.org/10.1023/a:1006496831144

Titolo: Treosulfan chemotherapy for recurrent malignant glioma.

Autori: Schmidt F., Wick W., Herrlinger U., Dichgans J., Weller M.

Data di Pubblicazione: 2001-2-24

Abstract: Treosulfan is a bifunctional alkylating prodrug with activity against various solid tumors. To improve the outcome for patients with recurrent malignant glioma, we assessed the efficacy of intravenous treosulfan (6-10 g/m<sup>2</sup> 4-weekly) as salvage therapy for patients with recurrent or progressive glioblastoma (GB, n = 14) or anaplastic astrocytoma (AA, n = 2). All patients had prior involved-field radiotherapy and adjuvant nitrosourea-based chemotherapy. A total of 56 cycles were administered. Tumor responses were assessed radiologically and clinically prior to each cycle. All patients were assessable for toxicity, response and survival. There were no complete or partial responses (CR, PR). Two patients progressed after the first cycle, 14 patients had initially stable disease (SD). Median progression-free survival was 3.25 months for the GB patients. Five patients were progression-free at 6 months (30%), including the 2 AA patients. The 2 AA patients are stable at 22 months. Myelosuppression was the dose-limiting toxicity in this cohort of nitrosourea-pretreated patients. Treosulfan has modest activity in patients with recurrent malignant glioma. Further evaluation of treosulfan in chemonaive malignant glioma patients is warranted.

Journal Title: Journal of neuro-oncology

PUBMED ID: 11149242

DOI: doi.org/10.1080/01616412.2000.11740756

Titolo: Analysis of the proliferative potential of tumor cells after stereotactic radiosurgery for recurrent astrocytic tumors.

Autori: Koder T., Kubota T., Kabuto M., Nakagawa T., Takeuchi H., Arishima H., Sato K., Kobayashi H., Kitabayashi M., Hirose S.

Data di Pubblicazione: 2001-1-10

Abstract: We analyzed the effectiveness of stereotactic radiosurgery (SRS) for recurrent astrocytic tumors histologically. Five patients were followed by pathological examination after radiosurgery treatment of recurrent astrocytic tumors. Histological diagnoses at the time of the last operation before SRS were Daumas-Duport grade II in two patients and grade IV (glioblastoma) in three patients. No histological diagnoses at the time of SRS were identified in any patients. Contrast enhanced lesions enlarged gradually on magnetic resonance (MR) images after SRS, and local control by SRS was judged as progressive disease radiologically in all patients. Four of five patients received re-operation after SRS, and the other patient died without re-operation and underwent post-mortem examination. After SRS, Ki-67 labeling indices (LIs) of recurrent astrocytomas initially diagnosed as grade II were 2.6% and 1.1%. These LIs were relatively lower than those of the control group of patients with recurrent grade II astrocytomas that were not treated by SRS. Ki-67 LIs of three glioblastomas after SRS were 23.5%, 18.6%, and 17.8%. These LIs were significantly lower than those before SRS (2.3%, 4.5%, and 0.9%). In the autopsy case, there was a significant difference between the LI of tumor cells in the radiosurgically treated region (0.9%) and that in the untreated region (29.2%). These results suggest that the proliferative potential of malignant astrocytic tumors in the radiosurgically treated area is reduced after SRS, and that radiological enlargement of enhanced lesions on MR images is due to propagation of the residual tumor cells that were not covered by radiosurgical target volume or to radiation necrosis. SRS may be a useful therapeutic tool in multidisciplinary treatment of malignant gliomas.

Journal Title: Neurological research

PUBMED ID: 11130015

DOI: doi.org/10.1080/028418600750063839

Titolo: Radiation therapy approach in gliomatosis cerebri--case reports and literature review.

Autori: Horst E., Micke O., Romppainen ML., Pyhtinen J., Paulus W., Schäfer U., Rube C., Willich N.

Data di Pubblicazione: 2000-12-29

Abstract: Gliomatosis cerebri is defined as a remarkably diffuse glioma, characterized by widespread infiltration of the central nervous system. Clinico-pathologic characteristics and imaging findings have been published but valid classification remains controversial. Few reports exist regarding therapeutic options in gliomatosis cerebri. Here we review data on 17 patients treated with radiation therapy extracted from the literature, in which we focus our attention on available details of irradiation and clinical outcome and present the results of three additional patients treated at our two institutions. Radiologic-pathologic correlation in gliomatosis cerebri indicates that tumor delineation should be based on T2-weighted MRI. Radiation therapy in gliomatosis cerebri is associated with a temporary improvement in or stabilization of clinical symptoms in the majority of cases. Duration of improvement was  $\geq 6$  months in 50% of treated patients. Survival from onset of symptoms was 23.8 months (range 8-42). Considerable variation in the natural course of the disease precludes conclusions regarding the impact of radiation therapy on survival.



Journal Title: Acta oncologica (Stockholm, Sweden)

PUBMED ID: 11096362

DOI: doi.org/10.1159/000028996

Titolo: Optic pathway hypothalamic gliomas in children under three years of age: the role of chemotherapy.

Autori: Silva MM., Goldman S., Keating G., Marymont MA., Kalapurakal J., Tomita T.

Data di Pubblicazione: 2000-11-30

Abstract: A majority of OPHGs responds to chemotherapy. Due to slow progression of these tumors and adverse effects of other therapeutic modalities, we recommend chemotherapy as a primary treatment for OPHGs. Our present data indicates that partial surgical resection does not enhance chemotherapy effectiveness for OPHGs in infants or children younger than 3 years.

Journal Title: Pediatric neurosurgery

PUBMED ID: 11066055

DOI: doi.org/10.1002/1097-0142(20001115)89:10<2131::aid-cncl14>3.0.co;2-j

Titolo: Oral trofosfamide and etoposide in pediatric patients with glioblastoma multiforme.

Autori: Wolff JE., Mölenkamp G., Westphal S., Pietsch T., Gnekow A., Kortmann RD., Kuehl J.

Data di Pubblicazione: 2000-11-7

Abstract: This chemotherapy will not be used in a randomized trial of patients with glioblastoma; however, it may be evaluated for patients with tumors that have more chemoresponsive histologies.

Journal Title: Cancer

PUBMED ID: 11014538

DOI: doi.org/10.3171/jns.2000.93.4.0605

Titolo: Prognostic factors in intracranial ependymomas in children.

Autori: Figarella-Branger D., Civatte M., Bouvier-Labit C., Gouvernet J., Gambarelli D., Gentet JC., Lena G., Choux M., Pellissier JF.

Data di Pubblicazione: 2000-10-3

Abstract: This study and analysis of the literature further highlight that total tumor removal is the treatment of choice for ependymomas in children. Postoperative measurement of residual tumor is required, especially because a subgroup of patients might be treated by surgery alone. Median infratentorial ependymomas have to be distinguished from the lateral type. Appropriate and reproducible histological parameters and Ki-67 LI are of interest as predictors of outcome.

Journal Title: Journal of neurosurgery

PUBMED ID: 10994549

DOI: doi.org/10.1055/s-2000-9676

Titolo: Boswellic acids in the palliative therapy of children with progressive or relapsed brain tumors.

Autori: Janssen G., Bode U., Breu H., Dohrn B., Engelbrecht V., Göbel U.

Data di Pubblicazione: 2000-9-20

Abstract: 19 children and adolescents with intracranial tumors received a palliative therapy with H 15 at a maximum dose of 126 mg/kg BW/day. All patients had previously been treated with conventional therapy. No side effects were observed during a median 9 months application. The recently reported anti-edematous effect of H 15 was documented by MRI in one patient with a peritumoral edema, thus sparing steroid therapy with its typical side effects. Five/19 children reported an improvement of their general health status; this mi

ght be a psychological effect of hope for tumor response during palliative care. Three/17 patients with malignant tumors showed a mainly transient improvement of neurological symptoms such as pareses and ataxia. Three further patients showed an increased muscular strength and one cachectic patient achieved a weight gain. These improvements might be attributed to the antiedematous effect of H 15. Because of the palliative situation of these patients, H 15 application was performed without prior rebiopsy for histological evaluation. Overlapping effects with a previous radiotherapy or chemotherapy may have occurred. An antiproliferative effect cannot be stated. To prevent an uncritical use of H 15, further studies with prospective central documentation have to be initiated to evaluate the clinical indications for H 15 in palliative therapy, optimal dosage and duration of application.  
Journal Title: Klinische Padiatrie

PUBMED ID: 10994547

DOI: doi.org/10.1055/s-2000-9674

Titolo: [HIT-LGG: effectiveness of carboplatin-vincristine in progressive low-grade gliomas of childhood--an interim report].

Autori: Gnekow AK., Kaatsch P., Kortmann R., Wiestler OD.

Data di Pubblicazione: 2000-9-20

Abstract: Combination therapy with Carboplatin and Vincristine can effectively delay the start of radiotherapy in children with progressive low-grade glioma. The high rate of hypersensitivity reactions has to prompt future modifications of treatment.

Journal Title: Klinische Padiatrie

PUBMED ID: 10987250

DOI: doi.org/10.1053/hupa.2000.9086

Titolo: Quantitative telomerase expression in glioblastomas shows regional variation and down-regulation with therapy but no correlation with patient outcome.

Autori: Kleinschmidt-Demasters BK., Evans LC., Bobak JB., Lopez-Urbe D., Hooper D., Shroyer AL., Shroyer KR.

Data di Pubblicazione: 2000-9-15

Abstract: Despite the nearly ubiquitous expression of telomerase in almost all types of malignant human tumors, studies have shown widely varying positivity in the highest-grade glioma, the glioblastomas (GBMs), ranging from 26% to 100% of tumors analyzed. We have previously shown significant variability in positive versus negative telomerase expression from region to region within the same GBM. In this study, we hypothesized that application of new quantitative methodology would extend our previous observations and identify whether there is heterogeneity in levels of protein expression even within areas positive for telomerase in high-grade gliomas. Finally, we sought to correlate quantitative telomerase expression with patient outcome and therapeutic response. Quantitative analysis was achieved by polymerase chain-based TRAP assay with phosphorimager analysis and compared with clinical information obtained from 19 patients, most with primary, untreated GBMs. Results showed up to 3-fold variability in telomerase levels across multiple regional samples from the same patient, as well as between patients. In 5 of 6 patients with recurrent tumors who had received intervening radiation therapy or chemotherapy, telomerase was downregulated in the second, post-therapy sample. These data provide in vivo corroboration of recent in vitro experiments showing telomerase downregulation after radiation therapy or chemotherapy treatment of cell lines. Our finding of variability in levels of telomerase expression in GBMs parallels the known heterogeneity of these tumors for histologic features and cell growth-related factors. Statistical analysis showed no relationship between TRAP score and either time to clinical progression or time to death.

Journal Title: Human pathology

PUBMED ID: 10955504

DOI: doi.org/10.1111/j.1740-8261.2000.tb02091.x

Titolo: Primary irradiation of canine intracranial masses.

Autori: Spugnini EP., Thrall DE., Price GS., Sharp NJ., Munana K., Page RL.

Data di Pubblicazione: 2000-8-24

Abstract: Twenty-nine dogs received primary radiation therapy for intracranial lesions and clinical signs suggestive of neoplasia. Presumptive diagnosis and tumor categorization was based on computed tomographic or magnetic resonance images. Meningioma was the most likely tumor type in 22 dogs and glioma or choroid plexus tumors were tentatively identified in 4 and 3 dogs, respectively. Cobalt-60 radiation was delivered in 3 Gy fractions on a daily, Monday-through-Friday basis for a total dose of 48 Gy (16 fractions) in 28 dogs; one dog received 54 Gy. Two of 29 dogs died during treatment of signs suggestive of progressive tumor growth but were included in the overall evaluation of response to treatment. Median overall survival was 250 days (range 21-804). Mild acute radiation effects on normal tissue developed and did not influence outcome in any dog. Late radiation effects could not be evaluated in this study. No significant predictive indicators were identified from the clinical or imaging data. Radiation therapy is superior to medical treatment of brain tumors in dogs with steroids, is useful for tumors that are not currently operable and may be preferable to surgical resection in dogs if the mass appears infiltrative. However, 22/29 (76%) dogs died of recurrent progressive neuropathy suggestive of tumor regrowth or progression. Thus, alternative methods for delivery of radiation to dogs with brain tumors or novel combinations of therapy should continue to undergo evaluation.

Journal Title: Veterinary radiology & ultrasound : the official journal of the American College of Veterinary Radiology and the International Veterinary Radiology Association

PUBMED ID: 10933931

DOI: doi.org/10.1006/mthe.2000.0030

Titolo: Phase I study of adenoviral delivery of the HSV-tk gene and ganciclovir administration in patients with current malignant brain tumors.

Autori: Trask TW., Trask RP., Aguilar-Cordova E., Shine HD., Wyde PR., Goodman JC., Hamilton WJ., Rojas-Martinez A., Chen SH., Woo SL., Grossman RG.

Data di Pubblicazione: 2000-8-10

Abstract: Between December 1996 and September 1998, 13 patients with advanced recurrent malignant brain tumors (9 with glioblastoma multiforme, 1 with gliosarcoma, and 3 with anaplastic astrocytoma) were treated with a single intratumoral injection of  $2 \times 10^9$ ,  $2 \times 10^{10}$ ,  $2 \times 10^{11}$ , or  $2 \times 10^{12}$  vector particles (VP) of a replication-defective adenoviral vector bearing the herpes simplex virus thymidine kinase gene driven by the Rous sarcoma virus promoter (Adv.RSVtk), followed by ganciclovir (GCV) treatment. The VP to infectious unit ratio was 20:1. Our primary objective was to determine the safety of this treatment. Injection of Adv.RSVtk in doses  $\leq 2 \times 10^{11}$  VP, followed by GCV, was safely tolerated. Patients treated with the highest dose,  $2 \times 10^{12}$  VP, exhibited central nervous system toxicity with confusion, hyponatremia, and seizures. One patient is living and stable 29.2 months after treatment. Two patients survived >25 months before succumbing to tumor progression. Ten patients died within 10 months of treatment, 9 from tumor progression and 1 with sepsis and endocarditis. Neuropathologic examination of postmortem tissue demonstrated cavitation at the injection site, intratumoral foci of coagulative necrosis, and variable infiltration of the residual tumor with macrophages and lymphocytes.

Journal Title: Molecular therapy : the journal of the American Society of Gene Therapy

PUBMED ID: 10894368

DOI: doi.org/10.1023/a:1006258026274

Titolo: Evaluation of pre-radiotherapy cyclophosphamide in patients with newly diagnosed glioblastoma multiforme. Writing Committee for The Brain Tumor Center at Duke.

Autori: Bottom KS., Ashley DM., Friedman HS., Longee DC.

Data di Pubblicazione: 2000-7-14

Abstract: Cyclophosphamide is an alkylating agent that has shown activity in the treatment of pediatric brain tumors, including high-grade gliomas. This study was designed to evaluate the response of patients with newly diagnosed glioblastoma multiforme to pre-radiotherapy cyclophosphamide. Fourteen patients with glioblastoma multiforme were treated with high-dose cyclophosphamide (2 g/m<sup>2</sup>/day for 2 doses every 28 days) followed by either sargramostim or filgrastin. Sargramostim was given 250 microg/m<sup>2</sup> subcutaneously twice a day continuing through the leukocyte nadir until the absolute neutrophil count was more than 1000 cells/microl for 2 consecutive days. The filgrastin dose was 10 microg/kg given subcutaneously once daily until the post nadir absolute neutrophil count was  $\geq$  10,000 cells/microl. A total of 46 courses was given. Four patients received a total of 3 courses, 7 patients completed 4 courses and 3 patients received 2 courses. Three patients demonstrated complete response; 3 stable disease; and 8 progressive disease. The most common toxicity was hematologic, requiring platelet and packed red blood cell transfusions, with 13 admissions for neutropenia with fever. There were no deaths related to infection or bleeding. These results suggest that high-dose cyclophosphamide has modest activity with acceptable toxicity against newly diagnosed glioblastoma multiforme.

Journal Title: Journal of neuro-oncology

PUBMED ID: 10871815

DOI: doi.org/10.1007/BF02796204

Titolo: Phase II study of temozolomide in patients with relapsing high grade glioma and poor performance status.

Autori: Janinis J., Efsthathiou E., Panopoulos C., Samantas E., Aravantinos G., Christodoulou C., Skarlos D.

Data di Pubblicazione: 2000-6-29

Abstract: Temozolomide (SCHS2.365), an oral alkylating agent which penetrates the blood-brain barrier, evolved as an alternative to dacarbazine. The aim of this study was to evaluate the efficacy and safety of temozolomide in terms of overall survival, progression-free survival, clinical benefit and health related quality of life in symptomatic patients with relapsing malignant glioma and a poor performance status. Eleven patients were enrolled in the study. The median age was 44.6 years. Patients were treated with temozolomide per os at a dose of 150-200 mg/m<sup>2</sup> daily for 5 consecutive days. Each cycle was repeated every 28 days. The median number of courses given per patient was 3.5. Nine patients were assessable for response. All patients were evaluable for toxicity. Based on radiographic findings 4 patients had stable disease (2 patients after a total of 16 cycles, and 2 patients after a total of 10 cycles). Four patients had progressive disease after 2 to 4 cycles. Of these 3 patients demonstrated a clinical benefit and one patient died after 3 cycles of treatment. Six patients had a significant clinical benefit even after 2 cycles of treatment with improvement of their neurological and performance status. Hematologic toxicity Gr II-III occurred in 3/9 patients. Nonhematologic toxicity consisted of Gr I nausea, and vomiting. In conclusion temozolomide appears to be a useful alternative for patients with relapsing malignant glioma after radiation and surgery and a poor performance status with little or no toxicity and considerable clinical benefit.

Journal Title: Medical oncology (Northwood, London, England)

PUBMED ID: 10864056

DOI: doi.org/10.1097/00043426-200005000-00010

Titolo: Tamoxifen and carboplatin for children with low-grade gliomas: a pilot study at St. Jude Children's Research Hospital.

Autori: Walter AW., Gajjar A., Reardon DA., Thompson SJ., Langston JW., Jones-Wallace D., Kun LE., Heideman RL.

Data di Pubblicazione: 2000-6-23

Abstract: The median age at diagnosis was 5.3 years, the median age at initiation of chemotherapy was 8.3 years. Eight patients had tumors of the hypothalamus/optic pathway, two patients had thalamic tumors, and one patient each had tumors in the temporal lobe, tectum, and brain stem. Tumor histologic findings included fibrillary astrocytoma (n = 2), juvenile pilocytic astrocytoma (n = 6), and oligodendroglioma (n = 1). The best response to therapy was a partial response in two patients, stable disease in nine patients, and progressive disease in two patients. The overall survival at 3 years is 69%. The 3-year progression-free survival is 47%. Tamoxifen and carboplatin chemotherapy did not result in a significant number of objective responses in children with low-grade gliomas. The progression-free survival is similar to that of other published series. Nonmyelosuppressive agents such as tamoxifen deserve additional evaluation in the treatment of children with low-grade gliomas.

Journal Title: Journal of pediatric hematology/oncology

PUBMED ID: 10837936

DOI: doi.org/10.1016/s0360-3016(00)00471-5

Titolo: A detrimental effect of a combined chemotherapy-radiotherapy approach in children with diffuse intrinsic brain stem gliomas?

Autori: Freeman CR., Kepner J., Kun LE., Sanford RA., Kadota R., Mandell L., Friedman H.

Data di Pubblicazione: 2000-6-6

Abstract: The finding that patients who received cisplatin given as a radiosensitizing agent concurrent with HRT fared less well than those receiving the same dose of HRT alone was unexpected and is clearly a cause for concern as many current protocols for patients with diffuse intrinsic brain stem gliomas call for use of chemotherapeutic and/or biological agents given concurrent with radiotherapy.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 10778730

DOI: doi.org/10.1023/a:1006293606710

Titolo: Pilot study of local autologous tumor infiltrating lymphocytes for the treatment of recurrent malignant gliomas.

Autori: Quattrocchi KB., Miller CH., Cush S., Bernard SA., Dull ST., Smith M., Gudeman S., Varia MA.

Data di Pubblicazione: 2000-4-25

Abstract: A prospective pilot study was performed in order to assess the safety of treating recurrent malignant gliomas (MGs) with locally infused autologous tumor infiltrating lymphocytes (TILs) and recombinant interleukin-2 (rIL-2). Six patients were entered between June 27, 1994 and June 2, 1995 and followed until July 1, 1998. At surgery an Ommaya reservoir was placed for later infusion of TILs and rIL-2. Following surgery, autologous TILs were expanded in vitro in the presence of rIL-2 and infused on treatment days 1 and 14, with concurrent rIL-2 infusions performed three times each week for one month. Following completion of immunotherapy all patients were offered chemotherapy. Phenotypic analysis demonstrated TILs to be T-lymphocytes (87-99% CD3+). Of these, 4 of 6 cases (67%) phenotyped as cytotoxic/suppressor T-lymphocytes.

hocytes (CD8+) and 2 of 6 cases (33%) phenotyped as helper/inducer T-lymphocytes (CD4+). TILs demonstrated limited selective cytotoxicity, with dose dependent cytotoxicity against autologous tumor, allogenic tumor and long term MG cell lines. There were no significant (Grade 3 or 4) complications. One patient developed transient low grade fevers, and 2 developed asymptomatic hydrocephalus. All patients developed transient and asymptomatic cerebral swelling, noted on the immediate post-treatment imaging studies. At three and six month follow-up, 3 patients responded with partial response, 2 demonstrated stable disease and 1 patient progressed. At long term follow-up, 1 patient had a complete response (45 month follow-up), 2 had a partial response (48 and 47 month follow-up) and 3 patients expired as a result of progressive disease (at 12, 12 and 18 months following immunotherapy). A relationship between subsequent chemotherapy or extent of resection to outcome was not apparent but could not be excluded. This pilot study demonstrated that locally infused autologous TILs and rIL-2 could be delivered without serious toxicity. Further studies are indicated to determine the safety and long term efficacy of TIL immunotherapy.

Journal Title: Journal of neuro-oncology

PUBMED ID: 10769645

DOI: Mancante

Titolo: Hydroxyurea and trimidox enhance the radiation effect in human pancreatic adenocarcinoma cells.

Autori: Leyden D., Ahmed N., Hassan HT.

Data di Pubblicazione: 2000-4-19

Abstract: The present study demonstrates the superiority of hydroxyurea at non-cytotoxic doses compared to the other two recent RR inhibitors: gemcitabine and trimidox in radio-sensitising human pancreatic cancer cells. Hydroxyurea combined with radiation has significantly improved progression-free survival of advanced cervical cancer and glioblastoma patients and showed clinical benefit in combination with other chemotherapy drugs in advanced pancreatic cancer. The present results suggest the clinical use of hydroxyurea as a radiosensitiser in both pre- and post-operative chemo-radiotherapy in pancreatic cancer patients. Given the demonstrated potent radio-sensitising effect of hydroxyurea at non-cytotoxic doses when administered before or immediately after radiation and its low clinical toxicity, it should be feasible to administer hydroxyurea both before and after radiation in pancreatic cancer patients.

Journal Title: Anticancer research

PUBMED ID: 10738082

DOI: doi.org/10.1016/s0167-8140(00)00149-3

Titolo: Radiation therapy of optico-hypothalamic gliomas (OHG)--radiographic response, vision and late toxicity.

Autori: Grabenbauer GG., Schuchardt U., Buchfelder M., Rödel CM., Gusek G., Marx M., Doerr HG., Fahlbusch R., Huk WJ., Wenzel D., Sauer R.

Data di Pubblicazione: 2000-3-30

Abstract: Postoperative RT with a total dose above 45 Gy should be considered as standard treatment in OHG with documented progression. Close radiographic monitoring and lifelong yearly evaluation for the need of possible hormone replacement are strongly recommended.

Journal Title: Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology

PUBMED ID: 10659011

DOI: doi.org/10.3171/jns.2000.92.2.0249

Titolo: Treatment of progressive or recurrent pediatric malignant supratentorial brain tumors with herpes simplex virus thymidine kinase gene vector-producer cells followed by intravenous ganciclovir administration.

Autori: Packer RJ., Raffel C., Villablanca JG., Tonn JC., Burdach SE., Burger K., LaFond D., McComb JG., Cogen PH., Vezina G., Kapcala LP.

Data di Pubblicazione: 2000-2-5

Abstract: This Phase I study demonstrates that in vivo gene therapy in which a replication-defective retroviral vector in murine vector-producing cells is delivered by brain injections can be performed with satisfactory safety in a select group of children with localized supratentorial brain tumors.

Journal Title: Journal of neurosurgery

PUBMED ID: 10649264

DOI: doi.org/10.1002/(sici)1097-0142(20000201)88:3<685::aid-cnrcr27>3.0.co;2-k

Titolo: Radiotherapy followed by high dose busulfan and thiotepa: a prospective assessment of high dose chemotherapy in children with diffuse pontine gliomas.

Autori: Bouffet E., Raquin M., Doz F., Gentet JC., Rodary C., Demeocq F., Chastagner P., Lutz P., Hartmann O., Kalifa C.

Data di Pubblicazione: 2000-1-29

Abstract: For patients with diffuse pontine gliomas, survival using this aggressive treatment modality does not appear to be any better than that reported for conventional radiotherapy.

Journal Title: Cancer

PUBMED ID: 10629654

DOI: Mancante

Titolo: Chemotherapy response rates in recurrent/progressive pediatric glioma; results of a systematic review.

Autori: Huncharek M., Wheeler L., McGarry R., Geschwind JF.

Data di Pubblicazione: 2000-1-12

Abstract: The optimum treatment strategy for recurrent childhood glioma is unknown. This report presents a systematic analysis of the currently available clinical data on chemotherapeutic management of this disease. A study protocol was prospectively developed outlining the objectives and methods of analysis including literature search strategy, eligibility criteria for published trials to be included, key data elements to be extracted and a plan for statistical analysis. Summary statistics were analyzed for the primary outcome variables. Data on recognized prognostic factors were recorded in order to adjust the outcome measures for these factors. A total of 27 non-randomized clinical trials were included in the analysis. Studies were stratified into 6 chemotherapy classes based on the frequency of drug used across studies. Average median response (complete + partial) across all drug categories was approximately 14% (range 10.4-23.5%). Adding patients with stable disease to complete and partial responders at least doubled average median response rates. Time to tumor progression ranged from 29.4 weeks to 49.7 weeks. The most frequently used drugs were the platinum analogs which demonstrated a mean TTP of 42.0 = +/-23.4 weeks. Small sample sizes and the overall poor quality of the available data precluded definitive conclusions regarding the clinical impact of the various drug classes on the natural history of this disease.

Journal Title: Anticancer research

PUBMED ID: 10619500

DOI: doi.org/10.1023/a:1006399804896

Titolo: Treatment of meningeal gliomatosis.

Autori: Pradat PF., Hoang-Xuan K., Cornu P., Mokhtari K., Martin-Duverneuil N., Poisson M., Delattre JY.

Data di Pubblicazione: 2000-1-5

Abstract: To evaluate whether vigorous treatment is beneficial for patients with meningeal gliomatosis (MG) we reviewed the case records of 20 consecutive patients treated for a symptomatic MG in our center. All received systemic or intrathecal chemotherapy and six received additional cranial or spinal radiotherapy. Six patients (30%) achieved a partial response (one low-grade astrocytoma, two anaplastic astrocytomas, one anaplastic oligodendroglioma and two glioblastomas). In these cases, clinical improvement was associated with radiological improvement on CT scan or MRI in five and with a major cerebrospinal fluid improvement in three. Three patients (15%) were stable for 3 months or more and 11 (55%) had progressive disease. Median survival was longer for the responding patients (10 months) than for the other patients (2 months). This study suggests that some patients with MG may benefit from a treatment combining radiotherapy to symptomatic areas and chemotherapy with agents that cross the blood-brain barrier or are delivered directly into the CSF.

Journal Title: Journal of neuro-oncology

PUBMED ID: 10576660

DOI: doi.org/10.1038/sj.bjc.6690802

Titolo: Phase I dose-escalation and pharmacokinetic study of temozolomide (SCH 52365) for refractory or relapsing malignancies.

Autori: Brada M., Judson I., Beale P., Moore S., Reidenberg P., Statkevich P., Dugan M., Batra V., Cutler D.

Data di Pubblicazione: 1999-11-27

Abstract: Temozolomide, an oral cytotoxic agent with approximately 100% bioavailability after one administration, has demonstrated schedule-dependent clinical activity against highly resistant cancers. Thirty patients with minimal prior chemotherapy were enrolled in this phase I trial to characterize the drug's safety, pharmacokinetics and anti-tumour activity, as well as to assess how food affects oral bioavailability. To determine dose-limiting toxicities (DLT) and the maximum tolerated dose (MTD), temozolomide 100-250 mg m<sup>-2</sup> was administered once daily for 5 days every 28 days. The DLT was thrombocytopenia, and the MTD was 200 mg m<sup>-2</sup> day<sup>-1</sup>. Subsequently, patients received the MTD to study how food affects the oral bioavailability of temozolomide. When given orally once daily for 5 days, temozolomide was well tolerated and produced a non-cumulative, transient myelosuppression. The most common non-haematological toxicities were mild to moderate nausea and vomiting. Clinical activity was observed against several advanced cancers, including malignant glioma and metastatic melanoma. Temozolomide demonstrated linear and reproducible pharmacokinetics and was rapidly absorbed (mean T<sub>max</sub> approximately 1 h) and eliminated (mean t<sub>1/2</sub> = 1.8 h). Food produced a slight reduction (9%) in absorption of temozolomide. Temozolomide 200 mg m<sup>-2</sup> day<sup>-1</sup> for 5 days, every 28 days, is recommended for phase II studies.

Journal Title: British journal of cancer

PUBMED ID: 10561268

DOI: doi.org/10.1200/JCO.1999.17.7.2127

Titolo: Treatment of children with medulloblastomas with reduced-dose cranio spinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group Study.

Autori: Packer RJ., Goldwein J., Nicholson HS., Vezina LG., Allen JC., Ris M D., Muraszko K., Rorke LB., Wara WM., Cohen BH., Boyett JM.

Data di Pubblicazione: 1999-11-24

Abstract: These overall survival rates compare favorably to those obtained in studies using full-dose radiation therapy alone or radiation therapy plus



chemotherapy. The results suggest that reduced-dose craniospinal radiation therapy and adjuvant chemotherapy during and after radiation is a feasible approach for children with nondisseminated medulloblastoma.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 10404133

DOI: doi.org/10.1002/(sici)1096-9098(199907)71:3<167::aid-jso6>3.0.co;2-v

Titolo: Carboplatin and etoposide for recurrent malignant glioma following surgical and radiotherapy failure: A clinical study conducted at the Northern Israel Oncology Center.

Autori: Stein ME., Kuten A., Drumea K., Goldsher D., Tzuk-Shina Z.

Data di Pubblicazione: 1999-7-15

Abstract: This phase II regimen proved to be ineffective in recurrent malignant glioma. Further studies incorporating innovative drug regimens and schedules are warranted. J. Surg. Oncol., 1999;71:167-170.

Journal Title: Journal of surgical oncology

PUBMED ID: 10192340

DOI: doi.org/10.1016/s0360-3016(98)00501-x

Titolo: There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy.

Autori: Mandell LR., Kadota R., Freeman C., Douglass EC., Fontanesi J., Cohen ME., Kovnar E., Burger P., Sanford RA., Kepner J., Friedman H., Kun LE.

Data di Pubblicazione: 1999-4-7

Abstract: The major conclusion from this trial is that the hyperfractionated method of Rx 2 did not improve event-free survival ( $p = 0.96$ ) nor did it improve survival ( $p = 0.65$ ) over that of the conventional fractionation regimen of Rx 1, and that both treatments are associated with a poor disease-free and survival outcome.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 10069350

DOI: doi.org/10.4065/74.2.137

Titolo: Phase II study of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in patients with recurrent glioma.

Autori: Buckner JC., Malkin MG., Reed E., Cascino TL., Reid JM., Ames MM., Tong WP., Lim S., Figg WD.

Data di Pubblicazione: 1999-3-9

Abstract: Although we could not confirm any tumor regression in patients in this study, the small sample size precludes definitive conclusions about treatment efficacy. Antineoplaston-related toxicity was acceptable in most patients with appropriate dose modification, although severe neurocortical toxicity may occur. Steady-state plasma concentrations of phenylacetate with use of A10 and AS2-1 were similar to those reported with use of similar doses of phenylacetate alone.

Journal Title: Mayo Clinic proceedings

PUBMED ID: 9989521

DOI: doi.org/10.1016/s0360-3016(98)00370-8

Titolo: Concurrent twice-a-week docetaxel and radiotherapy: a dose escalation trial with immunological toxicity evaluation.

Autori: Koukourakis MI., Giatromanolaki A., Schiza S., Kakolyris S., Georgoulas V.

Data di Pubblicazione: 1999-2-16

Abstract: Docetaxel radiochemotherapy is a promising therapeutic approach for locally advanced cancer. The recommended dose of docetaxel for chest and pelvic cancer patients is 15 mg/m<sup>2</sup> twice a week. Patients with brain tumors can be safely treated with higher doses of docetaxel (23 mg/m<sup>2</sup> twice a week) without toxicity. The severe immunologic toxicity observed suggests that granulocyte-macrophage colony-stimulating factor (GM-CSF) and immunoglobulin administration may be important in the efficacy and tolerance of taxane-based radiochemotherapy. Randomized trials are required to assess whether the efficacy of docetaxel radiochemotherapy depends on the frequency of docetaxel administration during radiation treatment.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 9874184

DOI: doi.org/10.1023/a:1006175831785

Titolo: Acute leukemia following treatment of malignant glioma.

Autori: Perry JR., Brown MT., Gockerman JP.

Data di Pubblicazione: 1999-1-5

Abstract: We report two patients with acute myeloid leukemia (AML) following therapy for malignant glioma; one was a young woman treated heavily with alkylating agents for glioblastoma and the other a young man treated with high doses of procarbazine, lomustine, and vincristine (PCV) for anaplastic astrocytoma. We found 26 other examples of therapy related leukemia in adult and pediatric brain tumor patients. Including our two, there were 12 patients with malignant glioma; median interval from treatment to diagnosis of AML was 31 months. Nine adult malignant glioma patients all received nitrosoureas, some as the sole form of chemotherapy. No definite cases occurred after radiotherapy alone. Based upon analogy with other cancers, the cumulative dose of chemotherapy, especially alkylating agents, is the major risk factor for development of secondary AML. Agents implicated include carmustine (BCNU), lomustine (CCNU), and procarbazine. Conventional radiotherapy appears not to confer additional risk. Progressive macrocytosis, early dose reductions for thrombocytopenia, and refractory anemia may provide early diagnostic clues. Current glioma therapy is leukemogenic but the number of patients who survive the interval required to induce AML is small; nevertheless, the identification of chemosensitive types of glioma, and subgroups of patients who derive the most benefit from chemotherapy, may result in increasing numbers of patients at risk of long term complications. If regimens such as PCV continue to prove valuable in neurooncology the risk of leukemia will require integration into the clinical decision process. A search for more effective therapy with minimal mutagenicity remains critical.

Journal Title: Journal of neuro-oncology

PUBMED ID: 9861650

DOI: doi.org/10.1007/s001170050441

Titolo: [Brain stem glioma].

Autori: Wietelmann D., Schumacher M., Muendel J.

Data di Pubblicazione: 1998-12-23

Abstract: Brain-stem gliomas occur mainly in childhood and are localized in the mesencephalon, pons and medulla oblongata. Diagnosis is a domain of MRI, requiring T2, T1 and KM. CT shows hemorrhage and calcification well. The criteria are the primary site, size, tumor growth, brain-stem enlargement, delineation, intralesional structure, exophytic components and enhancement. Secondary criteria are herniation, hydrocephalus and liquorogenic seeding. In CT glioma are hypodense, in MRI hyperintense in T2 and hypointense in T1. Enhancement is seen in 25-60% and does not allow differentiation of tumor vs non-tumor or gradings. Factors influencing poor outcome are high grade, a short history, cranial nerve involvement, severe brain-stem enlargement, pontine si

te, diffuse growth and recurrency. The 5-year-survival rate is 30% (after radiation: focal tumors 85%, diffuse 20%). Most frequent are symptoms of brain pressure, cerebellum, cranial nerves and pyramidal tract. There is no agreement on whether biopsy is necessary or not. A diagnosis of tumor is highly suggestive if classical MRI findings fit the clinical history.

Journal Title: Der Radiologe

PUBMED ID: 9840382

DOI: doi.org/10.1007/s003810050275

Titolo: Diffuse brain stem gliomas. Are we improving outcome?

Autori: Shuper A., Kornreich L., Loven D., Michowitz S., Schwartz M., Cohen IJ.

Data di Pubblicazione: 1998-12-5

Abstract: We reviewed our experience with diffuse brain stem glioma (dBSG) to evaluate whether any improvement of outcome had occurred in our patients over the years. Of the 24 children referred to our department with suspected dBSG from 1981 to 1997, 5 had a different final diagnosis based on the clinical course. Mean survival in the remainder was 16+/-9.8 months from diagnosis. Survival increased with a longer interval from onset of symptoms to diagnosis (12.9+/-9.0 months with an interval of 1-4 weeks; 19.50+/-10.8 months with a longer interval). Visual symptoms at presentation were associated with a poorer prognosis. Survival was better in the 3- to 5-year age group (at diagnosis). Overall, a trend toward a slight improvement in survival was seen over the years, which we presumptively attribute to the introduction of intensive chemotherapy for these patients. We suggest that chemotherapy may be important in the management of dBSG until a better modality is found.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 9810441

DOI: doi.org/10.1007/s007010050176

Titolo: Gliomatosis cerebri: clinical features, treatment, and prognosis.

Autori: Kim DG., Yang HJ., Park IA., Chi JG., Jung HW., Han DH., Choi KS., Cho BK.

Data di Pubblicazione: 1998-11-12

Abstract: To clarify clinical features and to elucidate prognostic factors and prognosis, the authors retrospectively analyzed 16 cases of gliomatosis cerebri treated at Seoul National University Hospital between January 1988 and December 1995. Age at diagnosis ranged from 19 to 62 (median 34) years and male to female ratio was 10:6. Most presented with headache or seizure, and the mean duration of symptoms was 12.8 months. A poorly defined diffuse high signal intensity lesion, extending in T2-weighted images for two lobes or more, was the characteristic magnetic resonance (MR) image finding. On postcontrast T1-weighted MR imaging, focal enhancement of the lesion was detected in five cases. All patients underwent histological confirmation by craniotomy (9 cases) or stereotactic biopsy (7 cases). Histologically, all patients had compatible findings of gliomatosis cerebri which are the widespread infiltration of neoplastic glial cells with minimal destruction of pre-existing structures. After histological diagnosis, external radiation therapy was begun except in one case, who declined this treatment. Fourteen patients completed the whole procedure and received the planned dose (mean 5780 cGy). Median survival time after diagnosis was 38.4 months. In univariate analysis, the Ki-67 labelling index ( $> 1$ ) showed significant correlation with the length of survival ( $p = 0.006$ ). It is suggested that 1) gliomatosis cerebri can be diagnosed by a combination of MR imaging findings and histological examination; 2) histological diagnosis and external radiation therapy might be a good treatment modality; 3) the Ki-67 labelling index correlates significantly with survival time.

Journal Title: Acta neurochirurgica

PUBMED ID: 9802850

DOI: doi.org/10.1097/00006123-199811000-00035

Titolo: PCV chemotherapy for recurrent oligodendrogliomas and oligoastrocytomas.

Autori: Soffietti R., Rudà R., Bradac GB., Schiffer D.

Data di Pubblicazione: 1998-11-5

Abstract: These results suggest that chemotherapy with PCV is effective in the treatment of recurrent low-grade oligodendrogliomas and oligoastrocytomas.

Journal Title: Neurosurgery

PUBMED ID: 9740547

DOI: doi.org/10.1023/a:1006043332368

Titolo: A phase II study of temozolomide in advanced untreated pancreatic cancer.

Autori: Moore MJ., Feld R., Hedley D., Oza A., Siu LL.

Data di Pubblicazione: 1998-9-18

Abstract: Temozolomide (SCH 52365) is an imidazotetrazine derivative which exhibits broad spectrum activity against murine tumors and is structurally related to dacarbazine (DTIC). Temozolomide cytotoxicity is schedule dependent in vivo with a daily x 5 schedule showing the highest activity. Oral temozolomide is rapidly and completely absorbed with minimal interpatient and intrapatient variability in pharmacokinetics. Clinical studies have demonstrated activity against melanoma and glioma. The present study examined the activity of oral temozolomide against patients with pancreatic cancer. Patients with advanced pancreatic adenocarcinoma previously untreated with chemotherapy received temozolomide 200 mg/m<sup>2</sup>/day once daily orally for 5 days with cycles repeated every 28 days. There were 16 patients entered on study with 15 evaluable for response and toxicity. There were no responses seen in 15 evaluable patients with 14 manifesting progressive disease within 2 months of starting therapy. Toxicity was primarily hematological with 3 patients experiencing > or = grade 3 neutropenia and thrombocytopenia respectively. Other toxicities were relatively modest. In conclusion, temozolomide in the once daily x 5 schedule is inactive against adenocarcinoma of the pancreas.

Journal Title: Investigational new drugs

PUBMED ID: 9667273

DOI: doi.org/10.1200/JCO.1998.16.7.2522

Titolo: Methylphenidate therapy improves cognition, mood, and function of brain tumor patients.

Autori: Meyers CA., Weitzner MA., Valentine AD., Levin VA.

Data di Pubblicazione: 1998-7-17

Abstract: This study demonstrated improved patient function in the setting of a progressive neurologic illness. Methylphenidate should be more widely considered as adjuvant brain tumor therapy.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 9667268

DOI: doi.org/10.1200/JCO.1998.16.7.2486

Titolo: Myeloablative chemotherapy with autologous bone marrow rescue in young children with recurrent malignant brain tumors.

Autori: Guruangan S., Dunkel IJ., Goldman S., Garvin JH., Rosenblum M., Boyett JM., Gardner S., Merchant TE., Gollamudi S., Finlay JL.

Data di Pubblicazione: 1998-7-17

Abstract: Myeloablative chemotherapy with ABMR followed by additional external-beam irradiation appears to be an effective retrieval therapy for some young children with recurrent malignant brain tumors.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 9626222

DOI: doi.org/10.1200/JCO.1998.16.6.2202

Titolo: Iodine-131-labeled antitenascin monoclonal antibody 81C6 treatment of patients with recurrent malignant gliomas: phase I trial results.

Autori: Bigner DD., Brown MT., Friedman AH., Coleman RE., Akabani G., Friedman HS., Thorstad WL., McLendon RE., Bigner SH., Zhao XG., Pegram CN., Wikstrand CJ., Herndon JE., Vick NA., Paleologos N., Cokgor I., Provenzale JM., Zatlutsky MR.

Data di Pubblicazione: 1998-6-17

Abstract: The MTD for administration of 131I-labeled 81C6 into the SCRCs of previously irradiated patients with recurrent primary or metastatic brain tumors was 100 mCi. The dose-limiting toxicity was neurologic toxicity. We are encouraged by the minimal toxicity and survival in this phase I trial. Radio-labeled mAbs may improve the current therapy for brain tumor patients.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 9619354

DOI: doi.org/10.1097/00001622-199805000-00004

Titolo: Advances in brain tumor chemosensitivity.

Autori: Balmaceda C.

Data di Pubblicazione: 1998-6-10

Abstract: Despite advances in surgery and radiation, most malignant central nervous system tumors recur. Chemotherapy has assumed an important role in treatment, particularly for responsive tumors such as primary central nervous system lymphoma and oligodendrogliomas. The design of sound chemotherapeutic trials for brain tumors requires an understanding of drug resistance. Drug sensitivity may be improved in a variety of ways: through the use of agents at higher than conventional doses or in new treatment schedules, through the use of localized resistance to modulators, and even through genetic manipulation of malignant cells. As treatment with chemotherapy for central nervous system tumors becomes more successful, new measurements of tumor response may need to be developed to replace or complement standard criteria.

Journal Title: Current opinion in oncology

PUBMED ID: 9609290

DOI: doi.org/10.3171/jns.1998.88.6.0969

Titolo: Low-grade gliomas in children: tumor volume response to radiation.

Autori: Fisher BJ., Bauman GS., Leighton CE., Stitt L., Cairncross JG., MacDonald DR.

Data di Pubblicazione: 1998-6-3

Abstract: On the basis of this CT scan analysis of the response of low-grade gliomas in children to radiotherapy, the authors suggest that these lesions respond to radiation, as demonstrated by tumor shrinkage on serial imaging. Major or complete responses occur occasionally. However, low-grade gliomas in children mimic other benign brain tumors such as pituitary adenomas and meningiomas in that, although growth is frequently arrested after radiotherapy, residual tumor can persist for many years, illustrating that tumor shrinkage may not be a good measure of treatment efficacy. Nevertheless, radiation therapy can result in improvement of clinical symptomatology in association

with or independent of visible tumor reduction. As radiation treatment techniques become increasingly conformal and because studies indicate that lower doses of radiation may be equally effective, improvement of symptoms may be an important consideration when weighing treatment options, particularly in patients with residual or unresectable disease.

Journal Title: Journal of neurosurgery

PUBMED ID: 9584959

DOI: doi.org/10.3109/13550289809114522

Titolo: Management of malignant glioma: role of surgery in relation to multi modality therapy.

Autori: Black P.

Data di Pubblicazione: 1998-5-19

Abstract: The goals of surgery for malignant glioma are to establish a histological diagnosis and to achieve mechanical cytoreduction to reduce intracranial pressure (ICP) and possibly alter tumor kinetics. There is controversy concerning the question whether the glioma is a focal or diffuse process; it appears that there may be variability between the two extremes in individual cases. The question of the value of surgery has also been controversial. Review of the literature suggests that both early and long-term postoperative outcome after radical surgical resection are better than the results of either partial resection or simple biopsy, in terms of neurological status and duration of survival. Similarly, reoperation for recurrence of glioma offers a reasonable extension of quality survival. Despite the desirability of extensive cytoreductive surgery for malignant gliomas, the presence of viable infiltrative cells beyond the margins of the resection necessitate that surgery be a part of an aggressive multimodality therapeutic approach. Adjunctive measures to control the infiltrative component include newer forms of radiotherapy (such as stereotaxic radiosurgery) and newer delivery techniques for chemotherapy (agents impregnated in biodegradable polymers implanted in the tumor bed after surgical resection), and possibly immunotherapy and gene therapy as they may become feasible in the future. The strategy for management of malignant glioma thus consists of a combination of extensive surgical resection to reduce the accessible tumor burden, followed in rapid sequence by measures to control the infiltrative portion of the tumor. It is recommended that these measures be offered 'up front' rather than delaying treatment until there is clinical or radiographic evidence of tumor recurrence.

Journal Title: Journal of neurovirology

PUBMED ID: 9538158

DOI: doi.org/10.3892/or.5.3.597

Titolo: Quick response of advanced cancer to chemoradiation therapy with antineoplastons.

Autori: Tsuda H., Sata M., Kumabe T., Hara H., Eriguchi N., Sugita Y., Nagamatsu H.

Data di Pubblicazione: 1998-5-9

Abstract: Antineoplastons A10 and AS2-1 exhibit growth inhibition of cancer cells by diverse modes of action. We observed antitumor responses within 2-3 weeks of a combination treatment of chemoradiation therapy and antineoplastons A10 and AS2-1 in phase I clinical study being conducted in Kurume University Hospital. We reviewed 3 clinical cases of advanced cancer (multiple metastatic lung cancer, thalamic glioma and primary lung cancer) in which we believed antineoplaston A10 and AS2-1 may be contributing to the rapid antitumor response. The possible use of this combination for induction therapy in advanced cancer is discussed.

Journal Title: Oncology reports

PUBMED ID: 9549488

DOI: doi.org/10.1093/brain/121.1.59

Titolo: A study of medial pallidotomy for Parkinson's disease: clinical outcome, MRI location and complications.

Autori: Samuel M., Caputo E., Brooks DJ., Schrag A., Scaravilli T., Branston NM., Rothwell JC., Marsden CD., Thomas DG., Lees AJ., Quinn NP.

Data di Pubblicazione: 1998-4-29

Abstract: We have studied the effects of unilateral ventral medial pallidotomy in 26 patients with medically intractable Parkinson's disease with marked drug-induced dyskinesias. Preoperatively, all patients were assessed during one 5-day admission according to the Core Assessment Programme for Intracerebral Transplantation (CAPIT) protocol, including rating in the 'practically defined off' and 'best on' states before and during a single-dose levodopa challenge. Motor performance was assessed with subset categories of the Unified Parkinson's Disease Rating Scale (UPDRS), timed motor tests and a standard dyskinesia rating scale. Pallidotomy was performed under stereotaxic CT guidance with intra-operative extracellular microelectrode recording made from the basal ganglia. All patients were re-assessed 3 months postoperatively and a subgroup (n = 9) have so far also been re-assessed after 1 year. Pre- and postoperative performance scores were compared in order to determine which categories of performance improved postoperatively. Significance was accepted at  $P < 0.005$  in order to take into account the multiple number of comparisons performed. Patient medication was compared pre- and postoperatively and the morbidity associated with surgery was also recorded. The most significant improvement postoperatively was the diminution of 'on' dyskinesias contralaterally (67%,  $P = 0.0001$ ); however, ipsilateral (45%,  $P = 0.0006$ ) and axial (50%,  $P = 0.0008$ ) dyskinesias also improved. Contralateral to pallidotomy, the median 'off' motor UPDRS score improved by 27% ( $P = 0.001$ ) and a significant improvement was also observed in contralateral rigidity by 25% ( $P = 0.001$ ). There were trends towards improvement in contralateral tremor (33%,  $P = 0.016$ ) and bradykinesia (24%,  $P = 0.013$ ) scores. Ipsilateral rigidity improved by 22% ( $P = 0.005$ ), but other ipsilateral motor scores did not alter significantly. The 'off' gait/postural instability score and 'off' walking time showed marginally significant improvements by 7% ( $P = 0.007$ ) and 29% ( $P = 0.014$ ), respectively. On medication, no significant postoperative improvements in parkinsonism were detected. Anti-parkinsonian medication increased by 11% postoperatively. In the subgroup who were available for assessment 1 year postoperatively, responses were generally maintained. Two (7.7%) of the 26 patients had fatal complications (one cerebral haemorrhage and one haemorrhagic infarct) directly related to surgery. Among the remaining 24 patients, four (15.4% of the total 26) had major complications (two persisting and two transient). Ten patients (38.5%) had minor complications. The majority of the complications (major and minor) occurred in the earlier operated patients and the complication rate subsequently declined with increasing operative experience. The remaining 10 patients (38.5%) had no significant side-effects. One of these 10 patients died from an incidental malignant glioma 6 months postoperatively. These findings confirm that levodopa-induced dyskinesias are dramatically reduced following ventral medial pallidotomy and constitute the principal indication for pallidotomy. Improvements in underlying parkinsonism were of smaller magnitude. Pallidotomy may also offer some patients an opportunity to increase antiparkinsonian medication. Patient selection for medial pallidotomy should, therefore, be based largely on anticipated improvements in levodopa-induced dyskinesias, but this must be balanced against the associated morbidity and mortality.

Journal Title: Brain : a journal of neurology

PUBMED ID: 9548522

DOI: doi.org/10.1159/000121239

Titolo: Optic chiasm astrocytomas of childhood. 1. Long-term follow-up.

Autori: Medlock MD., Madsen JR., Barnes PD., Anthony DS., Cohen LE., Scott R M.

Data di Pubblicazione: 1998-4-21

Abstract: We reviewed 61 patients seen from 1975 to 1994 with a biopsy-confirmed optic chiasm astrocytoma or a characteristic clinical and imaging presentation. The mean age at diagnosis was 72 months, including 30 who were less than 5 years old. The mean tumor diameter at presentation was 31 mm among 54 tumors measured. Tumors involved the optic nerve in 41, hypothalamus in 38, optic tract in 15, and optic radiations in 2. Four patients, all with neurofibromatosis, received no treatment. Forty patients received conventional radiation therapy at a mean age of 89 months. Chemotherapy was given to 19 children and 7 of these were followed for greater than 1 year. Six of these 7 had progressive disease which required subsequent surgery and/or radiation therapy. Thirty-six patients underwent surgery. We restricted our analysis of outcome to those 38 patients followed for longer than 60 months. Development was normal in 13%, mildly disabled in 53%, severely disabled in 21% and dead in 13%. Children were severely disabled or dead in 47% if younger than 5 years at diagnosis, and 21% if older. There was no endocrine dysfunction in 18% and new endocrine failure was seen in 61%. More posterior tumors did not portend a poorer prognosis. Children less than 5 years old had a poorer prognosis. Neurofibromatosis did not have a marked effect on outcome. Intracranial hypertension was an indicator of a poor prognosis. No specific treatment modality was clearly superior in terms of long-term survival or improvement in quality of life.

Journal Title: Pediatric neurosurgery

PUBMED ID: 9548332

DOI: doi.org/10.1007/s003810050165

Titolo: Chemotherapy in low-grade astrocytoma management.

Autori: Castello MA., Schiavetti A., Varrasso G., Clerico A., Cappelli C.

Data di Pubblicazione: 1998-4-21

Abstract: The role of chemotherapy (CHT) in the management of low-grade astrocytoma (LGA) is still unclear. Nineteen children with nonresectable symptomatic LGA were treated with carboplatin (CBDCA) and etoposide (E). There were 15 newly diagnosed cases and 4 were relapses; 6 of the children were under 5 years old. In all children radiological evaluation by CT scan and/or MRI was performed after four courses of CHT. We observed complete response (CR) + minor response (MR) in 37% of these cases and an improvement in neurological symptoms in 63%. Radiological evaluation performed in 6 patients who received CHT for longer periods (8-12 courses) showed major responses (CR+PR) in 67%. Local radiotherapy (40 Gy) was administered after CHT in 14 cases, but in 3 of these radiotherapy was delayed for 2 years. Five patients did not receive radiotherapy. The overall survival was 58% after an average follow-up of 60 months. All patients with brain stem tumors died of progressive disease even though 3 of these had shown clinical improvement after chemotherapy. In conclusion, in the treatment of nonresectable symptomatic LGA, CHT with CBDCA associated with E can be used to postpone radiotherapy in young children and even to avoid radiotherapy in some cases.

Journal Title: Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery

PUBMED ID: 9531367

DOI: doi.org/10.1016/s0360-3016(97)00891-2

Titolo: Boron neutron-capture therapy (BNCT) for glioblastoma multiforme (GBM) using the epithermal neutron beam at the Brookhaven National Laboratory.

Autori: Chadha M., Capala J., Coderre JA., Elowitz EH., Iwai J., Joel DD., Liu HB., Wielopolski L., Chanana AD.

Data di Pubblicazione: 1998-4-8



Abstract: It is feasible to safely deliver a single fraction of BPA-based BNCT. At the dose prescribed, the patients did not experience any morbidity. To further evaluate the therapeutic efficacy of BNCT, a dose-escalation study delivering a minimum target volume dose of 17 Gy-Eq is in progress.  
Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 9524096

DOI: doi.org/10.1023/a:1005826323652

Titolo: High dose oral tamoxifen and subcutaneous interferon alpha-2a for recurrent glioma.

Autori: Chang SM., Barker FG., Huhn SL., Nicholas MK., Page M., Rabbitt J., Prados MD.

Data di Pubblicazione: 1998-4-2

Abstract: Chemotherapeutic regimens in present use for recurrent glioma have substantial toxicity. Activity against recurrent gliomas has been reported for both tamoxifen and interferon alpha, agents that have more acceptable toxicity profiles and that can be administered in an outpatient setting. We tested the efficacy and toxicity of the combination of high-dose tamoxifen and interferon alpha in adults with recurrent glioma in a phase II trial. Eligible patients had radiographically measurable recurrent gliomas of any grade after initial radiation therapy. Interferon-alpha [ $6 \times 10^6$  U subcutaneously three times per week] and tamoxifen (240 mg/m<sup>2</sup>/day orally) were administered continuously. Treatment response was assessed at 6 week intervals using clinical and radiographic criteria. Eighteen patients (11 males and 7 females) were enrolled. Median age was 41 years (range 23-61 years). All patients had gliomas that progressed after radiation therapy and nitrosourea chemotherapy. The histologic diagnosis of the original tumor was glioblastoma multiforme in 8 patients, anaplastic astrocytoma in 5 patients, astrocytoma in 4 patients and mixed malignant glioma in 1 patient. Reversible moderate to severe neurological toxicity manifested by dizziness and unsteady gait was seen at tamoxifen doses of 240 mg/m<sup>2</sup>/day. Although the initial tamoxifen dose was reduced to 120 mg/m<sup>2</sup>/day, moderate neurotoxicity was noted at this dose as well and the trial was closed early. The combination of oral tamoxifen (120 to 240 mg/m<sup>2</sup>/day) and subcutaneous interferon-alpha [ $6 \times 10^6$  U three times per week] was associated with significant neurotoxicity in this group of recurrent glioma patients, resulting in early study closure. Of 16 evaluable patients, 12 had progressive disease after one cycle of treatment, 3 had stable disease, and there was one minor response. Gradual dose escalation may be required if similar patients are to be treated with high dose tamoxifen in conjunction with interferon.

Journal Title: Journal of neuro-oncology

PUBMED ID: 9498252

DOI: doi.org/10.1007/s001170050314

Titolo: [Profile of ambulatory radiosurgery with the gamma knife system. 2: Report of clinical experiences].

Autori: Wowra B., Horstmann GA., Cibis R., Czempiel H.

Data di Pubblicazione: 1998-3-14

Abstract: Gamma Knife radiosurgery (GKRS) was applied in 500 consecutive treatments for 445 patients within 2 years. Indications were arterio-venous malformations (93 patients), schwannomas of cranial nerves (75 patients), meningiomas (79 patients; 73 of the tumors involving the skull base), pituitary adenomas (40 patients), craniopharyngiomas (13 cases), gliomas (13 cases), rare indications (12 cases), and brain metastases (126 patients). In arterio-venous malformations two complications were observed whereas two other patients underwent surgery due to intracranial hemorrhage in the latent period after GKRS. In all cases follow-up with MRI showed evidence of an active obliteration process. Out of 24 patients with a follow-up over 1 year, angiography

revealed complete obliteration in 9 patients so far. A partial obliteration was evidenced by MRI in 15 cases. In benign tumors (meningiomas and vestibular schwannomas) tumor control rates of 88% and 89% were achieved, respectively. Treatment related side effects were mild and rare; no facial palsy occurred after primary Gamma Knife treatment. GKRS was particularly effective in inoperable skull base meningiomas. Cerebral metastases were controlled in 89.5% by a single Gamma Knife treatment. The mean survival period was 11.8 months. In patients receiving a single Gamma Knife treatment the mean survival time was 9.1 months. For patients undergoing multiple (up to 5) sessions of GKRS (because of new tumors) the mean survival period was 17.2 months. MRI showed evidence of adverse radiation reactions in 10/124 patients (8.1%) which were symptomatic in 3 patients (0.8%). The results obtained in patients with cerebral metastases emphasize that GKRS alone is as effective as the combined treatment of these lesions by surgery and fractionated radiotherapy. Our results demonstrated an attractively high therapeutic gain factor of Gamma Knife treatment in key indications of radiosurgery.

Journal Title: Der Radiologe

PUBMED ID: 9371386

DOI: doi.org/10.1002/(sici)1096-911x(199801)30:1<28::aid-mpo9>3.0.co;2-2

Titolo: Carboplatin and etoposide with hyperfractionated radiotherapy in children with newly diagnosed diffuse pontine gliomas: a phase I/II study.

Autori: Walter AW., Gajjar A., Ochs JS., Langston JW., Sanford RA., Kun LE., Heideman R.

Data di Pubblicazione: 1997-11-26

Abstract: The use of concurrent carboplatin and etoposide with hyperfractionated radiation therapy did not appear to improve the survival in this group of children with diffuse pontine gliomas. The toxicity of this chemotherapy during radiation therapy was primarily hematologic and well tolerated. New approaches to the treatment of these tumors need to be investigated.

Journal Title: Medical and pediatric oncology

PUBMED ID: 9336136

DOI: doi.org/10.1016/s0360-3016(97)00359-3

Titolo: Childhood optic chiasm gliomas: radiographic response following radiotherapy and long-term clinical outcome.

Autori: Tao ML., Barnes PD., Billett AL., Leong T., Shrieve DC., Scott RM., Tarbell NJ.

Data di Pubblicazione: 1997-10-23

Abstract: Notable radiographic response may be observed years after irradiation. Radiation therapy provides excellent long-term tumor control and vision preservation or improvement in the majority of patients with progressive chiasmal gliomas.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 9256121

DOI: doi.org/10.1200/JCO.1997.15.8.2792

Titolo: Low-grade astrocytoma: a decade of experience at St. Jude Children's Research Hospital.

Autori: Gajjar A., Sanford RA., Heideman R., Jenkins JJ., Walter A., Li Y., Langston JW., Muhlbauer M., Boyett JM., Kun LE.

Data di Pubblicazione: 1997-8-1

Abstract: The overall survival in this series of pediatric low-grade astrocytomas is excellent. Age at diagnosis and tumor location, but not histology, had a significant impact on PFS. Efforts to improve treatment outcome should focus on young patients (< 5 years) and on those with central midline tumors. The majority of patients with completely resected hemispheric tumors were

monitored without further therapy, which supports attempted GTR of cerebral and cerebellar hemisphere low-grade astrocytoma.  
Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 9276356

DOI: doi.org/10.1016/s0360-3016(97)00134-x

Titolo: UKCCSG study of accelerated radiotherapy for pediatric brain stem gliomas. United Kingdom Childhood Cancer Study Group.

Autori: Lewis J., Lucraft H., Gholkar A.

Data di Pubblicazione: 1997-7-15

Abstract: The results of this study are comparable to previous outcomes of studies with conventional and hyperfractionated radiotherapy in poor-prognosis brain stem glioma. The fractionation regimen was shown to be tolerable with an acceptable morbidity profile. However, further research is required to improve the poor prognosis of these unfortunate children.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 9302376

DOI: doi.org/10.1046/j.1365-2265.1997.2211032.x

Titolo: Endocrine outcome in long-term survivors of low-grade hypothalamic/chiasmatic glioma.

Autori: Collet-Solberg PF., Sernyak H., Satin-Smith M., Katz LL., Sutton L., Molloy P., Moshang T.

Data di Pubblicazione: 1997-7-1

Abstract: Nearly all studies assessing the patients with different tumour therapy evaluate patients with different tumour types. This study investigates a specific and large population of patients with H/CG and correlates the different form of treatment with the endocrine outcome. Precocious puberty, in children with this tumour, is probably due to tumour location rather than oncolological therapy. Conversely, although endocrine deficiencies can be a result of tumour location, the major causes of endocrine abnormalities were field irradiation and tumour surgery. A notable finding not previously reported is that endocrine dysfunction occurs less often in neurofibromatosis patients treated conservatively. Furthermore, this study documents that a significant number of young children grew normally despite receiving brain irradiation of greater than 45 Gy.

Journal Title: Clinical endocrinology

PUBMED ID: 9215830

DOI: doi.org/10.1200/JCO.1997.15.7.2596

Titolo: Phase II study of continuous infusion carmustine and cisplatin followed by cranial irradiation in adults with newly diagnosed high-grade astrocytoma.

Autori: Grossman SA., Wharam M., Sheidler V., Kleinberg L., Zeltzman M., Yue N., Piantadosi S.

Data di Pubblicazione: 1997-7-1

Abstract: This chemotherapy regimen appears to have significant activity and may prolong survival in adults with newly diagnosed high-grade astrocytoma.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 9167741

DOI: doi.org/10.1097/00000421-199706000-00002

Titolo: Fractionated stereotactic radiotherapy with cis-platinum radiosensitization in the treatment of recurrent, progressive, or persistent malignant astrocytoma.

Autori: Glass J., Silverman CL., Axelrod R., Corn BW., Andrews DW.

Data di Pubblicazione: 1997-6-1

Abstract: External beam irradiation of malignant astrocytoma often provides temporary local tumor control, but dose is limited by potential toxicity to normal brain. Fractionated stereotactic radiotherapy (SRT) provides additional radiation to the tumor with less dose deposition in adjacent normal brain. We administered a potential radiosensitizer, cis-platinum (CDDP), to optimize the therapeutic index. CDDP (40 mg/m<sup>2</sup>) was given weekly, with SRT once or twice weekly, to 20 patients. One had a partial response, 11 stable disease, and eight progressed despite therapy. Acute toxicities were manageable. Five patients required surgery for tumor progression or radiation necrosis. Median response duration was 18.5 weeks and median survival was 55 weeks. SRT combined with CDDP is safe, with durable responses in some patients. Further investigations to determine optimal SRT and CDDP doses and scheduling are justified.

Journal Title: American journal of clinical oncology

PUBMED ID: 9153469

DOI: doi.org/10.1212/wnl.48.5.1336

Titolo: Chemotherapy response criteria in malignant glioma.

Autori: Grant R., Liang BC., Slattery J., Greenberg HS., Junck L.

Data di Pubblicazione: 1997-5-1

Abstract: No one has ever proven a relationship between the extent of response to chemotherapy in malignant glioma and time to progression or survival. We studied the predictive value of "imaging response" following two courses of nitrosourea-based chemotherapy in 136 patients with recurrent astrocytoma/malignant glioma. We performed image analysis by blinded side-to-side comparison of sequential studies, and categorized response into: partial response (PR) (>50% reduction), minor response (MR) (25-50% reduction), stable disease (SD) (<25% change), progressive disease (PD) (>25% increase). Patients with PR, MR, and SD did not differ with respect to time to progression (TTP) ( $p > 0.2$ ) or survival ( $p > 0.2$ ). Median TTP was 27 weeks for SD, 43 weeks for MR, and 30 weeks for PR. Patients with PD had a significantly reduced survival ( $p < 0.001$ ). Median survival was 21 weeks for PD, 53 weeks for SD, 63 weeks for MR, and 48 weeks for PR. The lack of relationship between response and TTP may be due to early relapses in patients with response, a cytostatic benefit of chemotherapy in some patients who do not have an objective response, or a relatively favorable natural history in some tumors that do not respond to chemotherapy. Our data do not support the validity of current response grading, assessed after two courses of chemotherapy. Further research and validation of response criteria is necessary.

Journal Title: Neurology

PUBMED ID: 9126887

DOI: doi.org/10.3171/jns.1997.86.5.0747

Titolo: Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas.

Autori: Packer RJ., Ater J., Allen J., Phillips P., Geyer R., Nicholson HS., Jakacki R., Kurczynski E., Needle M., Finlay J., Reaman G., Boyett JM.

Data di Pubblicazione: 1997-5-1

Abstract: The optimum treatment of nonresectable low-grade gliomas of childhood remains undecided. There has been increased interest in the use of chemotherapy for young children, but little information concerning the long-term efficacy of such treatment. Seventy-eight children with a mean age of 3 years (range 3 months-16 years) who had newly diagnosed, progressive low-grade g

liomas were treated with combined carboplatin and vincristine chemotherapy. The patients were followed for a median of 30 months from diagnosis, with 31 patients followed for more than 3 years. Fifty-eight children had diencephalic tumors, 12 had brainstem gliomas, and three had diffuse leptomeningeal gliomas. Forty-four (56%) of 78 patients showed an objective response to treatment. Progression-free survival rates were 75 +/- 6% at 2 years and 68 +/- 7% at 3 years. There was no statistical difference in progression-free survival rates between children with neurofibromatosis Type 1 and those without the disease (2-year, progression-free survival 79 +/- 11% vs. 75 +/- 6%, respectively). The histological subtype of the tumor, its location, and its maximum response to chemotherapy did not have an impact on the duration of disease control. The only significant prognostic factor was age: children 5 years old or younger at the time of treatment had a 3-year progression-free survival rate of 74 +/- 7% compared with a rate of 39 +/- 21% in older children ( $p < 0.01$ ). Treatment with carboplatin and vincristine is effective, especially in younger children, in controlling newly diagnosed progressive low-grade gliomas.

Journal Title: Journal of neurosurgery

PUBMED ID: 9049885

DOI: doi.org/10.1023/a:1005736104205

Titolo: Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen.

Autori: Prados MD., Edwards MS., Rabbitt J., Lamborn K., Davis RL., Levin VA.

Data di Pubblicazione: 1997-5-1

Abstract: Between March 9, 1984 and January 29, 1992, 42 children with newly diagnosed symptomatic or previously diagnosed progressive low-grade gliomas received outpatient chemotherapy as their primary treatment. This study was a single arm, phase II trial designed to estimate the time to tumor progression and toxicity of this regimen. Procarbazine, 6-thioguanine, and dibromodulcitol were given before lomustine (CCNU) and vincristine was given 1 and 3 weeks after CCNU. Patients were treated for six treatment cycles or until the tumor progressed, whichever came first. Twenty-three patients had juvenile pilocytic astrocytomas, 11 had astrocytomas, one had oligodendroglioma, one had ganglioglioma, and six had radiographically diagnosed low-grade gliomas. The mean age of the patients was 5 years (median, 3 years). The median time to treatment failure was 132 weeks (95% confidence interval: 106, 186 weeks). Only eight patients have died the estimated 5-year survival rate is 78% (95% confidence interval, 60% 87%). There were two episodes of grade 4 neutropenia, and three episodes of grade 4 thrombocytopenia. This regimen was safe, able to be delivered in the outpatient setting, and produced prolonged periods of disease stabilization in children with low-grade gliomas.

Journal Title: Journal of neuro-oncology

PUBMED ID: 9092863

DOI: doi.org/10.1097/00006123-199704000-00042

Titolo: Second-look surgery for incompletely resected fourth ventricle ependymomas: technical case report.

Autori: Foreman NK., Love S., Gill SS., Coakham HB.

Data di Pubblicazione: 1997-4-1

Abstract: For patients in whom complete excision of fourth ventricle ependymomas is not possible at initial surgery, second-look procedures may enable macroscopic clearance to be achieved with little morbidity. A larger study is needed to evaluate this approach to treatment.

Journal Title: Neurosurgery

PUBMED ID: 9045344

DOI: Mancante

Titolo: Intensive radiation therapy concurrent with up to 7-week continuous-infusion paclitaxel for locally advanced solid tumors: phase I studies.

Autori: Rosenthal DI., Okani O., Truelson JM., Fathallah-Shaykh H., Vuitch F M., Gazdar AF., Griener J., Landay M., Mendelsohn D., Tourville J., Hamilton L., Orr KY., McWhorter J., Carbone DP.

Data di Pubblicazione: 1997-2-1

Abstract: Patients with locally advanced solid tumors of the lung, head and neck, and malignant astrocytomas usually succumb to their disease despite aggressive standard therapy. Laboratory data suggest that the addition of 1.0 to 10 nmol/L paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ), a microtubule stabilizing drug, to radiation therapy may result in significant radiation sensitization, perhaps due to accumulation of cells at G2/M. Relatively low concentrations (1.0 to 10 nmol/L) appear to be optimal for direct cytotoxicity and radiosensitization in vitro. Within this dose range, more prolonged exposure seems to result in higher response rates. The phase I trials reported here are designed to test the combination of paclitaxel, administered by continuous intravenous infusion (24 hours a day, 7 days a week), and standard, curative-intent radiation therapy. The ultimate goal of this study is to improve local and systemic control and survival for patients with these three tumor types. To date, 39 evaluable patients are enrolled in this study; there has been no dose-limiting toxicity up to 6.5 mg/m<sup>2</sup>/d. Observed toxicities include anemia, lymphopenia, mucositis, and cutaneous toxicities.

Journal Title: Seminars in oncology

PUBMED ID: 9368733

DOI: doi.org/10.1016/s0936-6555(05)80071-8

Titolo: Intradural drop metastases in oligodendrogliomas.

Autori: Shah N., Pigott K., Bradford R.

Data di Pubblicazione: 1997-1-1

Abstract: The case history is presented of a patient with primary intracerebral oligodendroglioma, who received multiple therapies for local recurrence. Four years following the initial diagnosis, the patient presented with spinal cord compression due to intradural metastases. The patterns of recurrence and metastases in oligodendroglioma are discussed.

Journal Title: Clinical oncology (Royal College of Radiologists (Great Britain))

PUBMED ID: 9071906

DOI: doi.org/10.1016/s0959-8049(96)00369-3

Titolo: Etoposide and thiotepa followed by ABMT (autologous bone marrow transplantation) in children and young adults with high-grade gliomas.

Autori: Bouffet E., Mottolese C., Juvet A., Philip I., Frappaz D., Carrie C., Brunat-Mentigny M.

Data di Pubblicazione: 1997-1-1

Abstract: The addition of conventional chemotherapy to irradiation has improved the outcome of children with malignant gliomas. The application of high-dose chemotherapy has been proposed as a possible way to increase the response rate and thus the survival in children with malignant brain tumours. High-dose etoposide (500 mg/m<sup>2</sup>/day x 3) and thiotepa (300 mg/m<sup>2</sup>/day x 3) followed by bone marrow transplantation were given to 22 patients (age range 4-20 years) with newly diagnosed or recurrent high-grade glioma. The response rate in the 14 assessable patients was 29% with one complete and three partial responses. 5 patients had stable disease, and 5 progressive disease. 2 patients died of treatment-related toxicity. Only 3 patients remain alive disease free 54, 60 and 65 months after high-dose therapy. For children with high-grade

de gliomas, survival using high-dose chemotherapy is no better than that reported with conventional treatments.

Journal Title: European journal of cancer (Oxford, England : 1990)

PUBMED ID: 9816151

DOI: Mancante

Titolo: Treatment of recurrent malignant gliomas with high-dose 13-cis-retinoic acid.

Autori: Yung WK., Kyritsis AP., Gleason MJ., Levin VA.

Data di Pubblicazione: 1996-12-1

Abstract: Malignant gliomas account for more than 60% of all primary brain tumors in adults. Adjuvant chemotherapy in addition to radical surgery and radiation therapy has provided only a modest increase in survival. Retinoic acid has been shown to have growth-inhibitory activity against glioma cells in culture. This provides the rationale for a Phase II study using 13-cis-retinoic acid (CRA) in patients with recurrent malignant brain tumors. The objective of this study was to determine the clinical activity of CRA in patients with a histologically proven diagnosis of malignant brain tumor and documented progressive or recurrent disease after radiation and chemotherapy. Fifty patients with documented recurrent disease were treated with CRA as a single agent p.o. at a dose of 60-100 mg/m<sup>2</sup> per day. Three weeks of treatment were followed by 1 week of rest. Of the 43 patients who received more than 4 weeks of therapy, 3 (7%) achieved partial response, 7 (16%) achieved minor response, 13 (30%) remained stable, and 20 (47%) had disease progression. The median time from onset of treatment to disease progression for the whole group of 43 patients was 16 weeks (19 weeks for glioblastomas and 11 weeks for anaplastic glioma), whereas that for the 23 patients with partial response and minor response and who remained stable was 66 weeks, and that for the 20 patients with progressive disease was only 8 weeks. The median survival time for glioblastoma was 58 weeks, and 34 weeks for anaplastic astrocytoma. Toxicity was mainly dermatological, with dry skin and cheilitis. These preliminary results suggest that 13-cis-retinoic acid is active against malignant gliomas and is very well tolerated.

Journal Title: Clinical cancer research : an official journal of the American Association for Cancer Research

PUBMED ID: 9293545

DOI: doi.org/10.1159/000121121

Titolo: Medulloblastoma with brain stem involvement: the impact of gross total resection on outcome.

Autori: Gajjar A., Sanford RA., Bhargava R., Heideman R., Walter A., Li Y., Langston JW., Jenkins JJ., Muhlbauer M., Boyett J., Kun LE.

Data di Pubblicazione: 1996-10-1

Abstract: We studied the impact of gross total resection on progression-free survival (PFS) and postoperative morbidity in 40 children with locally advanced medulloblastoma characterized by tumor invading the brain stem. These patients represented 40% of children treated for newly diagnosed medulloblastoma at a pediatric oncology center over a 10-year period. All patients underwent aggressive initial surgical resection. Review of surgical and neuroimaging findings documented gross total resection in 13 cases, near-total resection (< 1.5 cm<sup>2</sup> residual tumor on imaging) in 14 cases, and subtotal resection (> than 50% resection with > or = 1.5 cm<sup>2</sup> residual) in 13 cases. Overall, 85% of patients had a > 90% resection. Subsequent therapy comprised craniospinal irradiation in all cases and chemotherapy on institutional or cooperative group protocols in 35 cases. At a median follow-up of 4 years, postirradiation PFS is 61% (SE = 10%). There was no difference in PFS for patients who underwent gross total resection compared to those with any detectable residual tumor (p > 0.70). The posterior fossa syndrome occurred in 25% of cases, and

had no apparent relationship to the extent of resection ( $p > 0.5$ , exact test). In this series, true gross total resection was not associated with a PFS advantage when compared to strictly defined near-total and subtotal resection. Although there was no operative mortality, the frequency of the posterior fossa syndrome is of concern and emphasizes the need for careful consideration of the risk/benefit ratio in the surgical approach to this subgroup of patients.

Journal Title: Pediatric neurosurgery

PUBMED ID: 8862843

DOI: doi.org/10.1017/s031716710003852x

Titolo: Focal midbrain glioma: long term survival in a cohort of 16 patients and the implications for management.

Autori: Hamilton MG., Lauryssen C., Hagen N.

Data di Pubblicazione: 1996-8-1

Abstract: Patients with focal midbrain gliomas require symptom control aimed at treatment of hydrocephalus, or mass effect from the tumor. However the extended survival of this population suggests that routine aggressive surgical debulking is often not required. Furthermore, the routine use of radiation therapy or chemotherapy for all such patients is questioned.

Journal Title: The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques

PUBMED ID: 8844206

DOI: doi.org/10.1089/hum.1996.7.12-1465

Titolo: Treatment of advanced CNS malignancies with the recombinant adenovirus H5.010RSVTK: a phase I trial.

Autori: Eck SL., Alavi JB., Alavi A., Davis A., Hackney D., Judy K., Mollman J., Phillips PC., Wheelodon EB., Wilson JM.

Data di Pubblicazione: 1996-8-1

Abstract: Primary CNS malignancies are responsible for approximately 12,000 deaths annually in the United States. There has been little change in the outcome for adults with malignant brain tumors over the past few decades, despite improvements in surgical techniques and advances in radiation therapy. These tumors are uniformly fatal one to two years after diagnosis. The morbidity and mortality of this disease arise from the effects of a locally invasive, non-metastasizing lesion. The patients may suffer from seizures, paralysis, incoordination, aphasia, confusion, memory loss, sensory deficits or visual loss, depending on the regions of the brain affected. In addition, they usually require large doses of corticosteroids early and late in their illness, and may experience disabling side effects of this treatment, such as edema, proximal myopathy, diabetes, fungal infections or deep vein thrombosis. Few patients in the older age group are able to work after the diagnosis. Most of the patients are incapable of self-care for several months before death. The localized transfer of new genes into cancer cells potentially permits the expression of proteins with specific biologic functions that may provide a means to alter the biology of tumor growth through a variety of mechanisms including increasing tumor immunogenicity, inducing the local expression of toxic agents, and sensitization of tumors to chemotherapeutic agents. Gene therapy with the transfer of the drug susceptibility gene Herpes virus thymidine kinase (HSV-TK) has shown promise in a number of animal models, including CNS tumors. This study will evaluate the use of adenovirus-mediated transfer of the HSV-TK gene into primary human brain tumors followed by systemic treatment with ganciclovir. The goals of this phase I study are to evaluate the overall safety and efficacy of this treatment and to gain insight into the parameters that may limit the general applicability of this approach. In this phase I study, patients with recurrent gliomas will receive stereotactic-guided injections of the virus into the brain tumor, followed by intravenous



s ganciclovir for 14 days. Patients eligible to undergo a palliative debulking procedure will receive the same treatment followed by resection on day 7. At the time of resection a second dose of virus will be administered intraoperatively into the residual, unresectable portion of the tumor, and intravenous ganciclovir will be continued for additional 14 days. Tissue removed at the time of resection will be analyzed for evidence of adenovirus infection, thymidine kinase expression and signs of inflammation. The size and metabolic activity of all tumors will be followed by volumetric MRI scans and Positron Emission Tomography Scans, respectively. Patients will be enrolled in groups of three, with each group receiving successively larger doses of adenovirus. This study will quantify the toxicity of this therapy, and provide evidence as to the duration of transgene expression and virus induced inflammation.

Journal Title: Human gene therapy

PUBMED ID: 8656261

DOI: doi.org/10.1200/JCO.1996.14.6.1922

Titolo: Response of recurrent medulloblastoma to low-dose oral etoposide.

Autori: Ashley DM., Meier L., Kerby T., Zalduendo FM., Friedman HS., Gajjar A., Kun L., Duffner PK., Smith S., Longee D.

Data di Pubblicazione: 1996-6-1

Abstract: This report demonstrates the activity of oral VP-16 in the treatment of a small cohort of pretreated patients with recurrent medulloblastoma. This form of administration of oral VP-16 was well tolerated and produced modest toxicity.

Journal Title: Journal of clinical oncology : official journal of the American Society of Clinical Oncology

PUBMED ID: 8640684

DOI: doi.org/10.1002/(SICI)1097-0142(19960515)77:10<2150::AID-CNCR28>3.0.CO;2-T

Titolo: Treatment of children with newly diagnosed brain stem gliomas with intravenous recombinant beta-interferon and hyperfractionated radiation therapy: a childrens cancer group phase I/II study.

Autori: Packer RJ., Prados M., Phillips P., Nicholson HS., Boyett JM., Goldwein J., Rorke LB., Needle MN., Sutton L., Zimmerman RA., Fitz CR., Vezina LG., Etcubanas E., Wallenberg JC., Reaman G., Wara W.

Data di Pubblicazione: 1996-5-15

Abstract: We conclude that r beta IF plus hyperfractionated therapy can be tolerated by children with newly diagnosed brain stem gliomas, although there is occasional dose-limiting hepatic, blood, and central nervous system toxicity. This therapy did not result in a higher rate of disease control.

Journal Title: Cancer

PUBMED ID: 8614371

DOI: doi.org/10.1002/(SICI)1096-911X(199605)26:5<367::AID-MPO10>3.0.CO;2-A

Titolo: Diffuse plasmacytosis in a child with brainstem glioma following multiagent chemotherapy and intensive growth factor support.

Autori: Csáki C., Ferencz T., Sipos G., Kopper L., Schuler D., Borsi JD.

Data di Pubblicazione: 1996-5-1

Abstract: The use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) in order to abrogate chemotherapy-induced neutropenia has become a routine part of many cancer treatment regimes. However, there are still very few data available about possible complications related to repeated or prolonged use of these agents in patients with malignant solid tumors. The authors report a child with brainstem glioma who received repeated cycles of multiagent chemotherapy with G- or GM-

-CSF support. During this period of 10 months, no clinical side effects were observed that could have been attributed to growth factor administration. However, postmortem histological examination revealed the presence of diffuse plasmacytosis, a rare hematological disorder in childhood. Undifferentiated plasma cells of nonmonoclonal origin could be demonstrated infiltrating bone marrow, lungs, and lymph nodes of the patient. Based on previously published in vitro and in vivo evidence on the interleukin-6 (IL-6)-mediated stimulatory effect of G- and GM-CSF on myeloma cell proliferation, the authors suggest a possible link between extensive growth factor support and the development of plasmacytosis in this patient.

Journal Title: Medical and pediatric oncology

PUBMED ID: 8777179

DOI: doi.org/10.1093/oxfordjournals.annonc.a010550

Titolo: Phase II study of topotecan in patients with recurrent malignant glioma. National Clinical Institute of Canada Clinical Trials Group.

Autori: Macdonald D., Cairncross G., Stewart D., Forsyth P., Sawka C., Wainman N., Eisenhauer E.

Data di Pubblicazione: 1996-2-1

Abstract: Topotecan in this dose and schedule has only modest activity in recurrent glioblastoma and anaplastic astrocytoma.

Journal Title: Annals of oncology : official journal of the European Society for Medical Oncology

PUBMED ID: 8571175

DOI: Mancante

Titolo: Hyperthermia--its actual role in radiation oncology. Part IV: Thermo-radiotherapy for malignant brain tumors.

Autori: Seegenschmiedt MH., Feldmann HJ., Wust P., Molls M.

Data di Pubblicazione: 1995-10-1

Abstract: The encouraging results of clinical trials may be biased by favourable tumor and patient selection. Randomized clinical trials comparing RT alone versus combined RT-HT for advanced and recurrent brain tumors are justified. Part I has covered biological and technical fundamentals of clinical hyperthermia and has been published in Strahlenther. Onkol. 168 (1992), 183-190. Part II has covered clinical fundamentals and results in superficial tumors of clinical hyperthermia and has been published in Strahlenther. Onkol. 169 (1993), 633-654. Part III has covered clinical rationale and results in deep seated tumors and has been published in Strahlenther. Onkol. 171 (1995), 251-264.

Journal Title: Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]

PUBMED ID: 7674024

DOI: doi.org/10.3171/jns.1995.83.4.0724

Titolo: Primary diffuse leptomeningeal oligodendroglioma. Case report.

Autori: Chen R., Macdonald DR., Ramsay DA.

Data di Pubblicazione: 1995-10-1

Abstract: The authors describe a case of a diffuse primary leptomeningeal oligodendroglioma in a 17-year-old girl who presented with raised intracranial pressure and hydrocephalus. She underwent imaging studies and a left frontotemporal craniotomy that revealed a cystic oligodendroglioma in the suprasellar cistern and spread of neoplastic cells to the spinal leptomeninges. The tumor showed little response to maximum radiotherapy and chemotherapy, and the patient died from complications of high-dose chemotherapy 2 years after diagnosis. Postmortem examination of the brain and spinal cord revealed diffuse meningeal infiltration by neoplastic cells and no evidence of an intraparenchymal tumor.

nchymal origin. Glial heterotopias were noted at several sites along the brain base, adding circumstantial support to the theory that leptomeningeal gliomas are derived from ectopic glial tissue in the subarachnoid space.

Journal Title: Journal of neurosurgery

PUBMED ID: 7897512

DOI: doi.org/10.3171/jns.1995.82.4.0536

Titolo: Low-grade gliomas of the cerebral hemispheres in children: an analysis of 71 cases.

Autori: Pollack IF., Claassen D., al-Shboul Q., Janosky JE., Deutsch M.

Data di Pubblicazione: 1995-4-1

Abstract: Low-grade gliomas constitute the largest group of cerebral hemispheric tumors in the pediatric population. Although complete tumor resection is generally the goal in the management of these lesions, this can prove difficult to achieve because tumor margins may blend into the surrounding brain. This raises several important questions on the long-term behavior of the residual tumor and the role of adjuvant therapy in the management of these lesions. To examine these issues, the authors reviewed their experience in 71 children with low-grade cerebral hemispheric gliomas who were treated at their institution between 1956 and 1991 and assessed the relationship between clinical, radiographic, pathological, and treatment-related factors and outcome. Only seven patients in the series died, one from perioperative complications, five from progressive disease, and one (a child with neurofibromatosis) from a second neoplasm. For the 70 patients who survived the perioperative period, overall actuarial survivals at 5, 10, and 20 years were 95%, 93%, and 85%, respectively; progression-free status was maintained in 88%, 79%, and 76%, respectively. On univariate analysis, the factor that was most strongly associated with both overall and progression-free survival was the extent of tumor resection ( $p = 0.013$  and  $p = 0.015$ , respectively). A relationship between extent of resection and progression-free survival was present both in patients with pilocytic astrocytomas ( $p = 0.041$ ) and those with nonpilocytic tumors ( $p = 0.037$ ). Histopathological diagnosis was also associated with overall survival on univariate analysis; poorer results were seen in the patients with nonpilocytic astrocytoma compared to those with other low-grade gliomas, such as pilocytic astrocytoma, mixed glioma, and oligodendroglioma ( $p = 0.021$ ). The use of radiotherapy was not associated with a significant improvement in overall survival ( $p = 0.6$ ). All three patients who ultimately developed histologically confirmed anaplastic changes in the vicinity of the original tumor had received prior radiotherapy, 20, 46, and 137 months, respectively, before the detection of malignant progression. In addition, children who received radiotherapy had a significantly higher incidence of late cognitive and endocrine dysfunction than the nonirradiated patients ( $p < 0.01$  and  $0.05$ , respectively). The authors conclude that children with low-grade gliomas of the cerebral hemispheres have an excellent overall prognosis. Complete tumor resection provides the best opportunity for long-term progression-free survival. However, even with incomplete tumor excision, long-term progression-free survival is common. (ABSTRACT TRUNCATED AT 400 WORDS)

Journal Title: Journal of neurosurgery

PUBMED ID: 7897511

DOI: doi.org/10.3171/jns.1995.82.4.0530

Titolo: Stereotactic radiosurgery for glioblastoma: a final report of 31 patients.

Autori: Masciopinto JE., Levin AB., Mehta MP., Rhode BS.

Data di Pubblicazione: 1995-4-1

Abstract: From February 1989 to December 1992, 31 patients who presented with an initial pathological diagnosis of glioblastoma multiforme underwent tumor debulking or biopsy, stereotactic radiosurgery, and standard radiation th

erapy as part of their primary treatment. Presenting characteristics in the 22 men and nine women included a median age of 57 years, Karnofsky Performance Scale score median of 80, and median tumor volume of 16.4 cm<sup>3</sup>. Stereotactic radiosurgery delivered a central dose of 15 to 35 Gy with the isocenter location, collimator size, and beam paths individualized by means of three-dimensional software developed at the University of Wisconsin. The peripheral isodose line varied from 40% to 90% with a median of 72.5% and a mode of 80%. The mean follow-up period was 12.84 months with a median of 9.5 months. Statistical analysis was performed using Kaplan-Meier analysis and log-rank comparison of risk factor groups. The parameters of age, initial Karnofsky Performance Scale score, and biopsy were significantly different in patient survival from debulking; but no difference was noted between single and multiple isocenters and patterns of steroid requirement. Radiographic recurrences were divided by location into the following categories: central (within central stereotactic radiosurgery dose), 0; peripheral (within 2 cm of central dose), 19; and distant (> 2 cm), 4. There is no evidence of recurrence in five surviving patients. Actuarial 12-month survival was 37%, with a median survival of 9.5 months. These values are similar to previous results for surgery and standard radiotherapy alone. The results suggest that the curative value of radiosurgery is significantly limited by peripheral recurrences.

Journal Title: Journal of neurosurgery

PUBMED ID: 8729851

DOI: Mancante

Titolo: [Extracerebral metastases of a glioblastoma, in the absence of surgery].

Autori: Chretien F., Gray F., Funalot B., Authier FJ., Peltier E., Lange F., Degos JD., Poirier J.

Data di Pubblicazione: 1995-1-1

Abstract: A 50 y.o. male presented with a right parietal tumor which was a glioblastoma on stereotactic biopsy. He was treated by radiation and steroids, with clinical improvement. Four months later, he presented with a left preauricular mass and cervical lymphadenopathy. CT scan showed destruction of the left mastoid and filling of the left tympanic cavity. One month later, he suffered progressive dyspnea. Chest X ray showed a mediastinal mass on the right side and numerous bilateral interstitial opacities in the lungs. A bronchial biopsy was inconclusive. His general condition worsened, and he died. Postmortem showed continuous neoplastic infiltration of the left part of the base of skull, extending into the neck. Numerous metastases were present in mediastinal lymph nodes, lung parenchyma, pleura and pleural aspect of the diaphragm. There were no subdiaphragmatic metastases. Neuropathological examination confirmed a poorly differentiated highly malignant glioblastoma with severe necrosis involving the internal part of the parietal lobe extending to the dura mater of the convexity and falx cerebri with invasion of the superior longitudinal sinus which was entirely occluded. The biopsy scar was not infiltrated. Visceral tumors were morphologically identical to the brain tumor. They were strongly GFAP positive and cytokeratin negative. Extraneural metastases of glioblastoma in the absence of surgery are uncommon in adults. Involvement of the dura mater and/or superior longitudinal sinus is an almost constant feature. In our case, this may have led to invasion of the base of skull and secondary regional, lymphatic, and hematogenous spread.

Journal Title: Archives d'anatomie et de cytologie pathologiques

PUBMED ID: 7673984

DOI: doi.org/10.1007/BF01059953

Titolo: Leukoencephalopathy associated with intra-arterial ACNU in patients with gliomas.

Autori: Tsuboi K., Yoshii Y., Hyodo A., Takada K., Nose T.

Data di Pubblicazione: 1995-1-1

Abstract: Thirty cases of gliomas treated by surgery, radiotherapy and intra-arterial (IA) ACNU were reviewed with a focus on the late side-effect known as leukoencephalopathy. All cases were classified into three groups; remission (10 cases), regrowth (15 cases) and leukoencephalopathy (5 cases) from their outcome. The average total doses of IA ACNU were 49.8 mg/sqm body surface area in the remission group, 157.3 mg/sqm in the regrowth group and 203.1 mg/sqm in the leukoencephalopathy group. There were significant differences in the total IA ACNU doses between the remission group and both regrowth and leukoencephalopathy groups, while no significant differences were noticed in the dose of radiation given. There was a correlation between the total dose of IA ACNU and the occurrence of leukoencephalopathy. An autopsy of a typical case of leukoencephalopathy revealed various degrees of myelin breakdown and thickening of arterial walls, which probably manifested progressive dementia accompanied by urinary incontinence and gait disturbance.

Journal Title: Journal of neuro-oncology

PUBMED ID: 7623074

DOI: doi.org/10.1007/BF01058464

Titolo: Phase II study of amonafide in patients with recurrent glioma.

Autori: Levitt R., Buckner JC., Cascino TL., Burch PA., Morton RF., Westberg MW., Goldberg RM., Gallagher JG., O'Fallon JR., Scheithauer BW.

Data di Pubblicazione: 1995-1-1

Abstract: Amonafide, a novel imide derivative with broad preclinical antitumor activity, achieves significant cerebrospinal fluid levels in animal models. In order to test its antitumor activity in patients with recurrent diffuse infiltrative glioma of the astrocytic and oligodendroglial type, we performed a phase II clinical trial. Of the 22 eligible and evaluable patients treated, 2 (9%) experienced tumor regression lasting more than one year. No other patients experienced tumor regression; one remained stable more than six months. Toxicities consisted primarily of myelosuppression, vomiting, and venous irritation at the infusion site. We conclude that amonafide has minimal activity in recurrent glioma patients. Further investigations are not warranted in this study population.

Journal Title: Journal of neuro-oncology

PUBMED ID: 8082086

DOI: doi.org/10.1002/1097-0142(19940915)74:6<1827::aid-cnrcr2820740628>3.0.co;2-q

Titolo: Outcome of children with brain stem gliomas after treatment with 7800 cGy of hyperfractionated radiotherapy. A Childrens Cancer Group Phase I/II Trial.

Autori: Packer RJ., Boyett JM., Zimmerman RA., Albright AL., Kaplan AM., Rorke LB., Selch MT., Cherlow JM., Finlay JL., Wara WM.

Data di Pubblicazione: 1994-9-15

Abstract: The results of this treatment regimen demonstrate that hyperfractionated radiotherapy, as delivered in this study to a total dose of 7800 cGy, is relatively well tolerated, but may result in prolonged steroid-use dependency and possible radiation-associated damage. Objective responses to treatment were seen in 34% of patients, but these results were not better than those seen at lower doses of hyperfractionated radiotherapy. There is no evidence that radiation to 7800 cGy results in improved survival for patients with diffuse intrinsic brain stem gliomas.

Journal Title: Cancer

PUBMED ID: 8151347

DOI: doi.org/10.3171/jns.1994.80.4.0681

Titolo: The long-term outcome in children with late-onset aqueductal stenosis resulting from benign intrinsic tectal tumors.

Autori: Pollack IF., Pang D., Albright AL.

Data di Pubblicazione: 1994-4-1

Abstract: Benign intrinsic tumors arising in the dorsal midbrain have long been recognized as a potential cause of late-onset aqueductal stenosis. Where histopathological studies of such lesions have been performed, the majority have been reported to be low-grade gliomas. Because these tumors often present with a paucity of neurological findings and a characteristic radiographic appearance and because there has been substantial uncertainty regarding their potential for long-term progression, the authors have routinely deferred biopsy and/or radiotherapy for these lesions until there has been clear-cut evidence of disease progression. Herein, the authors report their experience with 16 children manifesting this syndrome who were treated between 1979 and 1992. The patients ranged in age from 6 months to 14 years at presentation (median 9.75 years). In general, symptoms of increased intracranial pressure developed insidiously; three of the older children had exhibited profound macrocephaly since infancy, which predated the onset of other symptoms of hydrocephalus by several years. Only one of the 16 children showed evidence of brain-stem dysfunction at presentation, a partial Parinaud's syndrome that resolved following placement of a ventriculoperitoneal shunt. In 12 patients, the tumor was detected by magnetic resonance (MR) imaging at initial evaluation as a bulbous enlargement of the tectal plate. In four patients who presented before the advent of MR imaging, initial computerized tomography (CT) scans failed to delineate the tectal lesion convincingly; however, subsequent MR studies clearly demonstrated the presence of an intrinsic tectal mass. All 16 patients underwent cerebrospinal fluid diversion initially, with conservative management of the tectal lesion and close long-term follow-up monitoring. Four children ultimately demonstrated clinical signs of progressive tumor growth with the insidious onset of partial or complete Parinaud's syndrome, despite the presence of a functioning shunt. The median interval to symptom progression was 7.8 years from the time of shunt insertion and 11.5 years from the onset of initial symptoms and signs of hydrocephalus. Follow-up CT and MR studies demonstrated obvious tumor enlargement in three of the four patients who then underwent stereotactic or open biopsy. The histological diagnosis in these three was benign mixed glioma, anaplastic astrocytoma, and low-grade astrocytoma. All four patients with clinical evidence of disease progression were treated with conventional radiotherapy; the patient with an anaplastic astrocytoma also received focal stereotactic radiosurgery. These patients subsequently remained clinically stable, with three showing tumor regression and one showing stable disease on serial MR studies (median follow-up period from tumor progression, 4.25 years). (ABSTRACT TRUNCATED AT 400 WORDS)

Journal Title: Journal of neurosurgery

PUBMED ID: 8153288

DOI: Mancante

Titolo: Delayed cerebral radiation necrosis.

Autori: Morris JG., Grattan-Smith P., Panegyres PK., O'Neill P., Soo YS., Langlands AO.

Data di Pubblicazione: 1994-2-1

Abstract: The clinical features and long-term outcome of seven patients with delayed cerebral radiation necrosis (DCRN) are described. Radiotherapy had been given for pituitary tumour (1), astrocytoma (2), pinealoma (2), craniopharyngioma (1) and parotid carcinoma (1). The mean latency to onset of the first neurological symptoms was 22 months (range 6-40 months), and mean duration of follow-up was 86 months (range 60-126). Three patients died at a mean of 84 months after radiotherapy (range 62-98). A fourth patient probably died from metastatic disease. Three patients remain alive, albeit severely disa

bled, after 5-10 years. The illness typically ran a stepwise course, with fits and stroke-like episodes occurring against a background of progressive dementia and somnolence. CT and MRI scans showed progressive ventricular dilatation associated with cerebral atrophy and diffuse or focal changes in the white matter. Four patients had had two or more neurosurgical procedures after the radiotherapy. In only one of the seven patients was the diagnosis made at presentation. DCRN produces a distinctive clinical picture, yet remains a poorly recognized complication of cranial irradiation.

Journal Title: The Quarterly journal of medicine

PUBMED ID: 8084310

DOI: doi.org/10.1002/mpo.2950230507

Titolo: High-dose chemotherapy with marrow reinfusion and hyperfractionated irradiation for children with high-risk brain tumors.

Autori: Kedar A., Maria BL., Graham-Pole J., Ringdahl DM., Quisling RG., Mickle JP., Mendenhall NP., Marcus RB., Gross S.

Data di Pubblicazione: 1994-1-1

Abstract: Between November 1990 and March 1993, nine pediatric patients with newly diagnosed brain tumors having a high risk of failure with standard treatment received high-dose thiopeta/cyclophosphamide chemotherapy followed by autologous bone marrow infusion and involved-field hyperfractionated radiation therapy. The presenting diagnoses were brainstem glioma (BSG) [6], parietal mixed high-grade oligodendroglioma-astrocytoma [1], thalamic anaplastic astrocytoma [1], and high-grade parietal glioma [1]. Following chemotherapy there were two partial responses, one minor response, three with stable disease, and one with progressive disease. Responses were not evaluated in two patients who had toxic deaths. Following radiation two patients, one with brainstem glioma and one with anaplastic mixed glioma, achieved complete remission. The overall survival is no better than conventional therapy.

Journal Title: Medical and pediatric oncology

PUBMED ID: 8084309

DOI: doi.org/10.1002/mpo.2950230506

Titolo: Carboplatin and VP 16 in medulloblastoma: a phase II Study of the French Society of Pediatric Oncology (SFOP).

Autori: Gentet JC., Doz F., Bouffet E., Plantaz D., Roché H., Tron P., Kalifa C., Mazingue F., Sariban E., Chastagner P.

Data di Pubblicazione: 1994-1-1

Abstract: The purpose of this study is to evaluate the antitumor activity of combination carboplatin and etoposide in measurable medulloblastoma. From January '89 to January '92, 26 patients with medulloblastoma were included in a multicentric phase II study of 2 courses of carboplatin 160 mg/m<sup>2</sup>/d day 1 to day 5 and VP16 100 mg/m<sup>2</sup>/d day 1 to day 5. Median age was 10 years (19 months-14.5 years). First treatment was surgery alone in 1 patient, surgery + radiotherapy in 4 patients, surgery + chemotherapy in 2 patients less than 3 years old, surgery + radiotherapy + chemotherapy in 19 patients ("8 drugs in 1 day" based:17, SIOP I:1, SIOP II:1). Previous treatment included cisplatin (20 cases), carboplatin (1 case), and VP16 (7 cases). Measurable disease was evaluated by CT scan, MRI or myelogram and CSF. Response rate (RR) was 72 +/- 10%: 8 complete responses (CR), 10 partial responses (PR), 1 objective effect (OE), 6 progressive disease (PD), 1 non-evaluable. Thirty-six courses were evaluated for toxicity. Median duration of WHO grade 4 neutropenia was 8 days (0-23). One patient died at day 18 after the first course because of diffuse haemorrhage during septic aplasia. Five other non-life-threatening septicemias were recorded. Median number of platelet transfusions was 1 (0-4). One child who had achieved a PR after two courses died from CNS bleeding after the third course. This drug combination achieves a high response rate in childhood medulloblastoma. Severe toxicity has been mainly encountered in pre

viously heavily treated patients. Tolerance may be acceptable in newly diagnosed children, but careful hematological follow-up and platelet transfusion support are definitely mandatory.

Journal Title: Medical and pediatric oncology

PUBMED ID: 7807192

DOI: doi.org/10.1007/BF01052725

Titolo: High dose chemotherapy for the treatment of malignant brain tumors.

Autori: Petersdorf SH., Livingston RB.

Data di Pubblicazione: 1994-1-1

Abstract: Conventional treatment of malignant high grade gliomas includes maximal resection followed by external beam radiotherapy. The addition of adjuvant chemotherapy has provided little improvement in the median duration of survival for these patients, particularly those patients with glioblastoma multiforme. The failure of conventional dose chemotherapy to improve the outcome of patients with high grade brain tumors has led several investigators to utilize high dose chemotherapy in order to overcome the limited benefit seen with conventional dose therapy which is due to intrinsic drug resistance as well as the impermeability of blood brain barrier. The majority of published studies utilizing this approach suggest that the addition of high dose chemotherapy with bone marrow transplant is of marginal benefit. However, most of these trials include small numbers of patients with advanced, refractory disease. A few trials have been reported utilizing high dose therapy in an adjuvant setting and the data from these studies are somewhat more promising. This review will analyze these studies and also discuss possible modifications of this approach in order to improve this aggressive treatment for patients who otherwise would have a dismal prognosis.

Journal Title: Journal of neuro-oncology

PUBMED ID: 7519356

DOI: doi.org/10.1007/978-3-642-85039-4\_10

Titolo: Radiosurgery/stereotactic external beam radiotherapy for malignant brain tumours: the Royal Marsden Hospital experience.

Autori: Brada M., Laing R.

Data di Pubblicazione: 1994-1-1

Abstract: SRT is a high-precision technique of radiotherapy which delivers focused irradiation to small target volumes. In the context of external beam radiotherapy it can be described as stereotactically guided conformal radiotherapy. As the technique originated from neurosurgical technology, it has initially been limited to single fraction treatment. However, with the use of relocatable fixation devices the way ahead particularly in its application in the treatment of brain tumours is in fractionated SRT. Currently, single fraction SRT/radiosurgery is of proven value only in the treatment of small inoperable arteriovenous malformations. It is being exploited in the management of brain tumours but so far remains as experimental treatment. We have demonstrated that fractionated SRT in patients with gliomas is a non-invasive equivalent to brachytherapy and in patients with solitary metastases a non-invasive alternative to surgical excision. However, the treatment is not without side effects, and the long-term effectiveness and toxicity of SRT, particularly with the use of unconventional fractionation, is not defined. The future use of SRT in the treatment of brain tumours should not be guided simply by the technical possibilities but by a rational appraisal of all treatment options to achieve the best disease control, survival and toxicity. Although there is potential for benefit in a number of small tumours, SRT cannot at present be recommended as the primary treatment in any tumour. In addition, its use should be discouraged in the treatment of unbiopsied brain lesions and as the major form of treatment of pineal germinomas. The technology of stereotactic radiotherapy is evolving, and it is likely that SRT will be inte



grated into conventional radiotherapy practice to become simply a high-precision technique of radiotherapy delivery in everyday use.

Journal Title: Recent results in cancer research. Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer

PUBMED ID: 8407392

DOI: doi.org/10.1016/0360-3016(93)90228-n

Titolo: Final results of a study of escalating doses of hyperfractionated radiotherapy in brain stem tumors in children: a Pediatric Oncology Group study.

Autori: Freeman CR., Krischer JP., Sanford RA., Cohen ME., Burger PC., del C arpio R., Halperin EC., Munoz L., Friedman HS., Kun LE.

Data di Pubblicazione: 1993-9-30

Abstract: The results of treatment in terms of progression-free survival and overall survival are not significantly different (at  $p = .55$  and  $p = .46$ , respectively) from those obtained at the two previous dose levels. There is no evidence that higher doses of hyperfractionated radiotherapy given as in this study improve the outlook of patients with poor-risk brain stem gliomas.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 8339232

DOI: doi.org/10.1002/1097-0142(19930815)72:4<1414::aid-cnrcr2820720442>3.0.co;2-c

Titolo: Hyperfractionated radiation therapy (72 Gy) for children with brain stem gliomas. A Childrens Cancer Group Phase I/II Trial.

Autori: Packer RJ., Boyett JM., Zimmerman RA., Rorke LB., Kaplan AM., Albrigh t AL., Selch MT., Finlay JL., Hammond GD., Wara WM.

Data di Pubblicazione: 1993-8-15

Abstract: The radiographic response rate is encouraging; however, it cannot be concluded that hyperfractionated RT, at this dose schedule and total dose, is superior to conventional RT.

Journal Title: Cancer

PUBMED ID: 8514549

DOI: doi.org/10.1016/0360-3016(93)90973-y

Titolo: The effect of advanced age on the efficacy of radiation therapy for early breast cancer, local prostate cancer and grade III-IV gliomas.

Autori: Peschel RE., Wilson L., Haffty B., Papadopoulos D., Rosenzweig K., F eltes M.

Data di Pubblicazione: 1993-6-15

Abstract: This study strongly supports the use of standard radiation therapy programs for early breast and prostate cancer patients age 70 years or more. However, our study raises questions about the efficacy of radiation therapy in patients over the age of 70 years with Grade 3-4 gliomas.

Journal Title: International journal of radiation oncology, biology, physics

PUBMED ID: 8509817

DOI: doi.org/10.1007/BF01053933

Titolo: Intracranial ependymoma long term outcome, patterns of failure.

Autori: Kovalic JJ., Flaris N., Grigsby PW., Pirkowski M., Simpson JR., Roth KA.

Data di Pubblicazione: 1993-2-1

Abstract: We analyzed 31 patients with intracranial ependymoma, all verified by secondary neuropathology review. There were 12 patients with ependymomas and 19 patients with anaplastic ependymoma by the WHO classification. Eight patients received craniospinal irradiation, 22 patients received cranial irr

adiation alone, and one patient was treated with chemotherapy alone. The median follow-up time was 11 years. The 5- and 10-year progression-free survivals (PFS) were 60% and 48%. Those with anaplastic tumors had a decreased 10 year PFS over those with low grade lesions: 26% vs. 55% ( $p = 0.02$ ). Delivering spinal irradiation in addition to cranial irradiation did not improve outcome. There were relapses in 16 patients. All patients relapsed at the primary intracranial sites with no spinal failures. Patients treated with whole brain irradiation had decreased 10 year PFS over those treated with local fields: 19% vs. 64% ( $p = 0.006$ ). Those patients treated to  $\geq 50$  Gy had an improved long-term PFS ( $p = 0.04$ ). Multivariate analysis was undertaken with the following variables: extent of cranial irradiation, pathology, anatomic site of ependymoma, cranial irradiation dose, extent of surgery, and whether spinal irradiation was given. With PFS as the endpoint, only extent of cranial irradiation (favoring local fields) and pathology (favoring low grade ependymoma) were significant prognosticators. We conclude that carefully outlined local field irradiation is the therapy of choice, and elective spinal irradiation is of questionable benefit.

Journal Title: Journal of neuro-oncology

PUBMED ID: 8339393

DOI: doi.org/10.1007/BF00735928

Titolo: Postoperative chemotherapy without radiation in young children with malignant non-astrocytic brain tumours. A report from the Australia and New Zealand Childhood Cancer Study Group (ANZCCSG).

Autori: White L., Johnston H., Jones R., Mameghan H., Nayanar V., McWhirter W., Kellie S., Waters K., Toogood I.

Data di Pubblicazione: 1993-1-1

Abstract: Young children with malignant brain tumours have particularly poor survival and manifest severe sequelae of radiation therapy. A multi-institutional pilot study of post-operative primary chemotherapy for children under 3 years with primitive neuroectodermal tumours (PNET) or ependymoma was initiated in 1987. The chemotherapy protocol comprised carboplatin, vincristine and the "eight drugs in 1 day" regimen. Radiation was recommended only if tumour progression or recurrence was documented. A total of 14 patients between 5 and 36 months of age were enrolled. Seven had supratentorial tumours (PNET, pinealoblastoma, intracranial retinoblastoma) with multiple predictors of adverse outcome. Four of these responded to initial chemotherapy but subsequently progressed and all had died by 16 months from diagnosis. The seven patients with infratentorial tumours (three medulloblastomas, four ependymomas) had more favourable predictors of outcome: no meningeal dissemination and gross macroscopic resection in six of the seven cases. One patient progressed rapidly and died within 5 months. The other six are alive at 37-57 months from diagnosis. Four are in continuous complete remission at 57, 51, 41 and 37 months, respectively from the time of their tumour resection. One is described as having stable disease with a persistent radiographic lesion at 41 months from diagnosis. One has relapsed on two occasions and is the only surviving patient to have been irradiated. Intelligence scores for the six long-term survivors have thus far remained within the normal range. It is suggested that some infants with standard-risk ependymoma and, possibly, medulloblastoma may be cured without radiation therapy.

Journal Title: Cancer chemotherapy and pharmacology

PUBMED ID: 1460488

DOI: doi.org/10.1007/BF00172601

Titolo: Multiple-fraction-per-day external beam radiotherapy for adults with supratentorial malignant gliomas.

Autori: Halperin EC.

Data di Pubblicazione: 1992-11-1

**Abstract:** The prognosis following therapy for adults with supratentorial malignant gliomas is poor. Standard therapy of 60 Gy of external beam radiotherapy with chemotherapy achieves a median survival time of 35 to 51 weeks following surgery. A variety of innovative therapies have been considered for therapy of malignant gliomas. Multiple-fraction-per-day (MFD) external beam radiotherapy has been evaluated by many investigators. The rationale for MFD radiotherapy is based upon exploiting differences in the recovery capacity for radiation damage between slowly and rapidly proliferating tissues and/or shortening the overall treatment time. A large number of clinical trials have, for the most part, failed to show any survival benefit from MFD radiotherapy. These trials have utilized b.i.d. and t.i.d. radiotherapy with fraction sizes of 0.89 to 2 Gy to total doses of 30-81.6 Gy. The linear quadratic model of the radiation cell survival curve suggests that a biological effective tumoricidal dose  $\geq$  10% higher than standard daily radiotherapy, with approximately isoeffective normal tissue damage, could be achieved at 1.2 Gy b.i.d. to a total dose of approximately 72 Gy. Trials of low dose per fraction MFD radiotherapy, to total doses less than 72 Gy, would be predicted to be inadequate to the task.

**Journal Title:** Journal of neuro-oncology

PUBMED ID: 1432038

DOI: doi.org/10.1007/BF00177619

**Titolo:** Chemotherapy with vincristine (VCR) and etoposide (VP-16) in children with low-grade astrocytoma.

**Autori:** Pons MA., Finlay JL., Walker RW., Puccetti D., Packer RJ., McElwain M.

**Data di Pubblicazione:** 1992-10-1

**Abstract:** Twenty patients, aged 6 months to 20 years, with low-grade astrocytoma (LGA) participated in a chemotherapy trial of vincristine (VCR) and etoposide (VP-16). Fourteen children had recurrent progressive disease at entry on study. Prior treatment consisted of surgical resection alone (6), surgical resection and irradiation (4), surgical resection, irradiation and chemotherapy (2), surgery and chemotherapy (1), and irradiation and chemotherapy (1). Six patients were treated at initial diagnosis of LGA because they were less than 5 years old (5) or for a second primary tumor (1). Four recurrent patients and 3 newly diagnosed patients underwent surgical debulking of their tumors immediately prior to study entry. Tumors were located in the optic nerve/chiasm/hypothalamus (8), brain stem/cerebellum (4), cerebral hemispheres (3), midline structures (3), and spinal cord (2). The treatment plan administered in an out-patient setting consisted of weekly VCR 1.5 mg/m<sup>2</sup> for 7 to 8 weeks and VP-16 100 mg/m<sup>2</sup> for 5 days repeated every 6 weeks for a total of 18 months of therapy. Responses were evaluated by computerized tomography or magnetic resonance imaging. Of the 20 patients, 1 exhibited a partial response maintained for 12+ months, 3 exhibited minor responses maintained for a period of 10+ to 35 months, and 11 maintained stable disease for 10 to 42 months. Of the 11 patients with stable disease, 2 were withdrawn early from the study without further therapy. Five of the 20 patients developed progressive disease; for 4 of these 5, this occurred during the first course of therapy. Subsequently, these 5 died due to tumor. (ABSTRACT TRUNCATED AT 250 WORDS)

**Journal Title:** Journal of neuro-oncology

PUBMED ID: 1506881

DOI: doi.org/10.3171/jns.1992.77.3.0355

**Titolo:** Adult intramedullary astrocytomas of the spinal cord.

**Autori:** Epstein FJ., Farmer JP., Freed D.

**Data di Pubblicazione:** 1992-9-1

**Abstract:** In this series, 25 adult patients with intramedullary astrocytomas were treated by radical excision alone. Six patients proved to have anaplast

ic astrocytoma; five of them died within approximately 2 years and the sixth has demonstrated disease progression. The other 19 patients were diagnosed as having low-grade astrocytoma (16 cases) or ganglioglioma (three cases); two of these had advanced preoperative neurological disability and died of medical complications. Fifteen of the remaining 17 patients have no clinical evidence of tumor recurrence after a mean follow-up period of 50.2 months; the other two have a small residual neoplasm that demonstrates no progression. Of these 17 patients, seven had previously received radiation therapy, but had clear evidence of tumor growth subsequently. This experience suggests that surgery is not beneficial for anaplastic spinal astrocytoma. However, in cases of low-grade tumor, radical excision is associated with minimal morbidity and an excellent long-term prognosis when carried out before significant disability occurs.

Journal Title: Journal of neurosurgery

PUBMED ID: 1607975

DOI: doi.org/10.3171/jns.1992.77.1.0078

Titolo: Clinical effect of intra-arterial tumor necrosis factor-alpha for malignant glioma.

Autori: Yoshida J., Wakabayashi T., Mizuno M., Sugita K., Yoshida T., Hori S., Mori T., Sato T., Karashima A., Kurisu K.

Data di Pubblicazione: 1992-7-1

Abstract: Recombinant human tumor necrosis factor-alpha was administered intra-arterially to treat 20 cases of malignant gliomas, mostly progressive or recurrent. The optimum dosage was determined to be  $1 \times 10^5$  U/sq m/day. Among the 10 evaluable patients treated at this dosage, two responded (one completely and one partially), resulting in a 20% response rate. Side effects were mild and easily controllable. Improvement of neurological symptoms was noted in 47% of the patients a few days after treatment, even when computerized tomography showed no tumor regression. This might have been due to the pleiotypic biological activity of tumor necrosis factor-alpha. Neuroradiographic observations revealed narrowing of the tumor-feeding artery, a decrease in tumor staining ability, and necrosis in the central part of a tumor. The authors suggest that intra-arterial administration of tumor necrosis factor-alpha may be an effective treatment for malignant glioma, including recurrent cases.

Journal Title: Journal of neurosurgery

PUBMED ID: 1919696

DOI: doi.org/10.3171/jns.1991.75.5.0740

Titolo: Long-term outcome of 89 low-grade brain-stem gliomas after interstitial radiation therapy.

Autori: Mundinger F., Braus DF., Krauss JK., Birg W.

Data di Pubblicazione: 1991-11-1

Abstract: Between 1974 and 1985, 89 patients suffering from histologically confirmed, nonresectable low-grade astrocytomas located in the brain stem were entered into a retrospective study. Iodine-125 ( $^{125}\text{I}$ ) was implanted in 29 patients and iridium-192 ( $^{192}\text{Ir}$ ) in 26 patients. Computerized tomography revealed that 78% of the tumors in these patients were located chiefly in the mesencephalic region, 70% were circumscribed, and 78% were contrast-enhanced. Thirty-four patients underwent biopsy without prior aggressive tumor-specific therapy such as chemotherapy or external beam irradiation. Among these, 70% of the tumors were located predominantly in the pons, 74% were diffuse, and 59% were hypodense or isodense after contrast enhancement. Long-term follow-up investigations indicated that life expectancy after interstitial radiation therapy with  $^{125}\text{I}$  implanted directly by catheter either permanently or temporarily showed a more favorable trend than that after treatment with  $^{192}\text{Ir}$ . Interstitial radiation therapy with  $^{125}\text{I}$  appears to be an effective treat

ment for slowly proliferating, differentiated, well-delineated, nonresectable brain-stem gliomas. This technique makes it possible to achieve radiosurgical tumor control and, when carefully applied, represents the least traumatic treatment. Reduction of the tumor mass brings about improvement of the clinical symptoms. Further investigations on the biological behavior of brain-stem gliomas and prospective randomized long-term follow-up studies are necessary to evaluate the different kinds of treatment available for these patients.

Journal Title: Journal of neurosurgery