

High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

R. Stupp¹, M. Brada², M. J. van den Bent³, J.-C. Tonn⁴ & G. Pentheroudakis⁵ on behalf of the ESMO Guidelines Working Group*

¹Department of Oncology and Cancer Centre, University Hospital Zurich, Zurich, Switzerland; ²Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Clatterbridge Cancer Centre, Wirral, UK; ³Department of Neuro-Oncology, Erasmus MC Cancer Center, Rotterdam, Netherlands; ⁴Department of Neurosurgery, Ludwig-Maximilians-University, Munich, Germany; ⁵Department of Medical Oncology, Medical School, University of Ioannina, Ioannina, Greece

incidence and epidemiology

The yearly incidence of malignant glioma is ~3–5/100 000 with a slight predominance in males. Malignant glioma may develop at all ages, with the peak incidence being in the fifth and sixth decades of life [1–3].

Exposure to ionising irradiation has been associated with increased risk of development of glioma, while association with the use of cell phones could not be confirmed in epidemiological studies. Rare hereditary syndromes carry an increased risk for glioma: Cowden-, Turcot-, Lynch-, Li-Fraumeni syndrome and neurofibromatosis type 1.

diagnosis and pathology

The commonly used World Health Organization (WHO) classification distinguishes tumours according to their presumed cell of origin (astrocytes or oligodendrocytes), and grades them from grade I–IV [4]. Grade I tumours occur mainly in childhood, and grade II (or low-grade) glioma are slow-growing tumours but will almost invariably transform over time to a more malignant phenotype. Grade III tumours (also commonly referred to as anaplastic glioma) comprise anaplastic astrocytoma, mixed anaplastic oligoastrocytoma and anaplastic oligodendrogloma, while glioblastoma (GBM) represents WHO grade IV. Tissue diagnosis is mandatory, and usually obtained by stereotactic biopsy or after tumour resection. GBM carries the worst

prognosis, while pure oligodendrogloma has a protracted natural history and better outcome, and excellent response to therapy. Prognosis of mixed anaplastic oligoastrocytoma and anaplastic astrocytoma is intermediate between GBM and pure anaplastic oligodendrogloma.

Concordance between local diagnosis and central neuropathology review can be as low as 50%, thus careful review of the histology by an expert neuropathology

high-grade glioma; when observed in high-grade glioma, it suggests that the tumour has developed from a lower grade precursor lesion (secondary GBM) [9, 10]. Less than 10% of individuals with adult GBM carry an IDH mutation, while ~60% of grade III tumours are IDH-mutated [8, 11]; IDH-mutated tumours are associated with a more favourable prognosis [12, 13]. Indeed, the survival of IDH-mutated GBM is more favourable than for non-mutated grade III astrocytoma, thus underscoring the strong prognostic value of this finding [10, 12]. The more frequent IDH1 mutation accounts for ~90% of all IDH mutations and can be demonstrated by immunohistochemistry, while IDH2 mutations and IDH1 mutations at other sites can only be identified by sequencing. In lower grade tumours or suspected transformed glioma, IDH sequencing should be carried out if staining by immunohistochemistry with the anti-IDH antibody (which recognises R132H mutation) is negative.

Epigenetic silencing of the methyl-guanine methyl transferase (MGMT) gene promoter by gene promoter methylation suggests a partial inability of the tumour to repair the chemotherapy induced DNA damage [14]. In retrospective analyses, MGMT methylation has been correlated with a response to or benefit

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org

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team is recommended [5, 6]. Molecular markers are useful additional tools for diagnosis and treatment guidance (see below), and are of increasing importance in daily practice. Adequate tissue collection and preservation (e.g. sufficient material, fresh frozen tumour tissue) should be planned prospectively (see Table 1).

molecular markers

Genetic loss on chromosomes 1p/19q (co-deletion or loss of heterozygosity [LOH] 1p/19q) is a consequence of a chromosomal translocation and describes a distinct tumour entity characterised by a prolonged natural history irrespective of treatment, and increased sensitivity both to radiotherapy (RT) and to chemotherapy [7]. LOH 1p/19q should be evaluated to support a diagnosis of oligodendrogloma. Mutations of the isocitrate dehydrogenase gene (IDH) were recognised in 2008 as an early event in glioma genesis [8]. Mutations in the IDH gene 1 or 2 are hallmarks of

Table 1. Expected survival of glioma

Grade and cell type	Median survival
Grade II	
Astrocytoma	7–10 years
Oligodendrogloma ^a	>10–15 years
Grade III	
Anaplastic astrocytoma	3.5 years
Anaplastic oligodendrogloma ^a	>10 years
Grade IV	
Glioblastoma	15 months, 2-year survival 27% MGMT Methylated 23 months, 2-year survival: 49% Unmethylated 13 months, 2-year survival: 12%

^aWith LOH 1p/19q. MGMT, methyl-guanine methyl transferase

of alkylating agent chemotherapy [II, B] [15, 16]. MGMT determination by immunohistochemistry lacks standardisation, reproducibility and, most importantly, correlation with clinical outcome [III, C], while MGMT status determination by methylation-specific polymerase chain reaction (MSP) has been largely standardised and allows for reproducible results [17, 18]. A predictive value of a methylated MGMT status for response to or benefit from alkylating agent chemotherapy and thus improved outcome has been demonstrated repeatedly in GBM [19, 20]. However, in lower grade IDH-mutated tumours,

MGMT methylation identifies a sub-population with a better prognosis irrespective of the applied treatment [18].

The determination of these markers is now part of routine practice; however, whether MGMT methylation status determination is carried out for an individual patient depends on the diagnostic and therapeutic context (Table 2). In the absence of clinical consequences and better alternative treatments, MGMT status assessment may not be necessary for every patient [V, D]; nevertheless, in elderly patients improved outcome with adapted treatment strategy [i.e. temozolomide (TMZ) chemotherapy for MGMT-methylated tumours, radiotherapy for unmethylated tumours] has been demonstrated in two randomised trials [II, A] [19, 20]. In current clinical trials, MGMT status is always required as a stratification factor. For a detailed discussion, the reader is referred to recent extensive reviews [18].

These markers are neither mutually exclusive nor entirely independent. MGMT promoter methylation is highly associated with LOH 1p/19q and IDH mutations [11]. MGMT methylation is predictive for benefit from alkylating agent chemotherapy in GBM, while it confers a largely prognostic value in anaplastic grade III tumours. A recent report from the Neuro-Oncology Working Group (NOA) of the German Cancer Society confirmed a predictive value of MGMT methylation for benefit from chemotherapy in patients with a wild-type IDH, independent of tumour grade [21].

staging and risk assessment

Although glioma are invasive tumours with a strong propensity of glioma cells to migrate, tumour dissemination remains

limited to the central nervous system and distant metastases are virtually non-existent; thus, staging focuses on imaging of the brain, ideally by magnetic resonance imaging (MRI). The spine and cerebrospinal fluid (CSF) are not routinely assessed in the absence of clinical symptoms. Ideally, the extent of tumour resection and determination of residual disease should be assessed after surgery; however, this assessment must be carried out within 24–48 h in order to distinguish post-surgical contrast enhancement from residual tumour. Lower tumour grade, radical tumour resection, younger age (<50 years), good performance status and an intact neurological function are favourable prognostic factors. Determination of molecular markers (discussed above) will identify patients with a more favourable prognosis or better chance of response to alkylating agent chemotherapy.

disease management and treatment plan

general management

Patients should be evaluated and the treatment plan determined by a specialised multidisciplinary team including neurosurgeons, medical and radiation oncologists, but also an expert neuropathologist and neuroradiologist. Special consideration should be given to performance status and neurological function. Corticosteroids (usually dexamethasone 8–16 mg/day, but lower doses may be just as effective) allow for rapid reduction of tumour-associated oedema and improve clinical symptoms. Patients' glucose levels need to be

monitored. Steroids are not necessary in patients without increased intracranial pressure or in the absence of oedema-associated neurological deficits. There is no need for prolonged steroid therapy after tumour resection or for prophylaxis during radiotherapy in asymptomatic patients. Rapid tapering and discontinuation of corticosteroids is recommended in order to avoid toxicity associated with prolonged exposure to steroids, e.g. myopathy and weakness, lymphopenia and risk of infection, osteoporosis and Cushing syndrome.

Anti-epileptic therapy is indicated in patients presenting with seizures; however, prophylactic use of anticonvulsants outside the perioperative phase is not indicated [III, C]. After tumour resection, the indication for anti-seizure therapy should be revised only if seizures occur [22, 23]. First generation anti-epileptic drugs (phenytoin, carbamazepine, phenobarbital and their derivatives) are strong inducers of the hepatic metabolism, and may interfere with medications including many commonly used chemotherapy agents (but not with TMZ). Agents such as lamotrigine, levetiracetam, pregabalin or valproic acid are preferred.

Glioma patients are at increased risk of thromboembolic events due to a tumour-induced hyper-coagulable state, but also as a consequence of neurological deficits, immobilisation and steroid use [24]. Prophylactic anticoagulation is not recommended; however, a low threshold for excluding deep vein thrombosis and pulmonary emboli is indicated when suspicious symptoms occur. The presence of a brain tumour is not a contraindication for the use of standard anticoagulants in patients with proven thrombosis.

newly diagnosed patients

Surgery is commonly the initial therapeutic approach for tumour debulking and obtaining tissue for diagnosis. Tumour

MGMT promoter methylated^t

Reduced DNA repair, associated in IDH1/2-mutant tumours^c

MSP, MS or bisulphite (pyr)^r

40%–50%

60%–80%

50%

70%

35%

None^e

I
Prognostic for anaplastic gliomas (treated with r)

for benign^e

Predictive in GBM

Elderly GBM: MGMT-methylated^m unmethylated^d

RT

→

island methylator phenotype; IDH, isocitrate dehydrogenase; DD, differential diagnosis; MGMT, methylation element (FUSE) binding protein 1; FISH, fluorescence in situ hybridisation; DNA, deoxyribonucleic acid;

70

1p/19q co-deletionⁿ IDH1/2 mutationⁿ

Unclear, candidate genes CIC and FUBP¹. Increased levels of 2-hydroxyglutarate, link to Biological consequence^e under investigationⁿ G-CIMP phenotype^e

FISH, micro-satellite analysis for loss of^f Immunohistochemistry for IDH1-R132H; ^f Methods of assessment^t heterozygosity negative, gene sequencing^g

Frequency^y

WHO grade I^l

15%

70%–80%

Diffuse astrocytoma^a

30%–60%

70%–80%

Oligodendrogioma/

oligoastrocytoma^a

WHO grade II^l

15%

50%–70%

Anaplastic astrocytoma^a

50%–80%

50%–80%

Anaplastic^c

Oligodendrogloma^f

oligoastrocytoma^a

WHO grade IV^v

<5%

5%–10% Glioblastoma^a

Pathognomonic for oligodendrogloma^a DD glioma versus gliosis^s Diagnostic role^e

Typical for transformed low-grade glioma^a

Protracted natural history in 1p/19q codelete^d Protracted natural history in IDH-mutant^d Prognostic role^e

tumour^S tumour^S

Prolongation of survival with early chemotherapy^Y Absence of mutation suggests predictive role^E

Predictive role^E

in 1p/19-co-deleted oligodendrogloma^S for MGMT promoter methylation^N

WHO, World Health Organization; G-CIMP, glioma CpG

capicua transcriptional repressor; FUBP1, far upstream^M

methylation-specific; GBM, glioblastoma; TMZ, temozolomide; RT, radiotherapy.

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resection is of prognostic value; it may be beneficial to attempt maximal tumour resection provided that neurological function is not compromised by the extent of resection [II, C] [25]. An increase in the complete resection rate and improvement in progression-free survival (PFS) have been shown when surgery is carried out under blue light with the use of fluorescent marking of the tumour by 5-amino-laevulinic acid (5-ALA) [26]. When micro surgical resection is not safely feasible (e.g. due to location of the tumour or impaired clinical condition of the patient), a biopsy should be carried out. In experienced hands, the diagnostic yield is >95% [18]. A sufficient amount of tissue should be obtained for molecular analyses, and open biopsies may yield more tissue to allow this compared with stereotactic biopsies. On freshly frozen specimens, molecular genetic analyses (LOH 1p/19q, MGMT promoter methylation) can be carried out even with small amounts of tissue, and this should be planned beforehand [27].

Implantation of chemotherapy-impregnated wafers (carmustine polymers) into the resection cavity before radiotherapy has been shown to marginally improve median survival compared with radiotherapy alone [II, B] [28]; however, no prospective data are available when compared with current standard TMZ/RT (see below) [29]. An increase in wound healing and infectious complications has been reported. The combination of carmustine wafers and TMZ/RT has not been assessed in prospective trials, a retrospective comparison failed to

demonstrate additive efficacy [IV, D] [30].

Fractionated localised radiotherapy (60 Gy, 30–33 fractions of 1.8–2 Gy, or equivalent doses/fractionations) is part of the standard treatment after resection or biopsy [I, A] [31]. Escalating doses beyond 60 Gy have not been shown to be of value. In elderly patients or patients with a low performance status, shorter hypo-fractionated regimens (e.g. 40 Gy in 15 fractions) are commonly proposed [II, B] [32]. Radiotherapy (28 × 1.8 Gy, 50 Gy) in patients >70 years of age was superior to best supportive care alone in a randomised phase III trial [II, B] [33]. Exclusive TMZ chemotherapy has shown an improved outcome compared with radiotherapy alone in elderly patients with a methylated MGMT gene promoter in two randomised trials [II, A] [19, 20] (see Figure 1).

glioblastoma (WHO grade IV)

Concomitant and adjuvant TMZ chemotherapy in addition to radiotherapy (TMZ/RT → TMZ) significantly improved median, 2- and 5-year survival in a large randomised trial, and is the current standard of care for patients with GBM up to age 70 [34, 35] [I, A], or fit elderly patients older than 70 years [II, B] [36]. TMZ is administered daily (7 days a week) during radiotherapy and for 5 days every 4 weeks for six cycles as maintenance (adjuvant) treatment after the end of radiation. MGMT gene promoter methylation has been demonstrated as the strongest prognostic marker for outcome, and the added benefit of TMZ

1° GBM

Grade IV
Prior lower grade

Rapid onset:

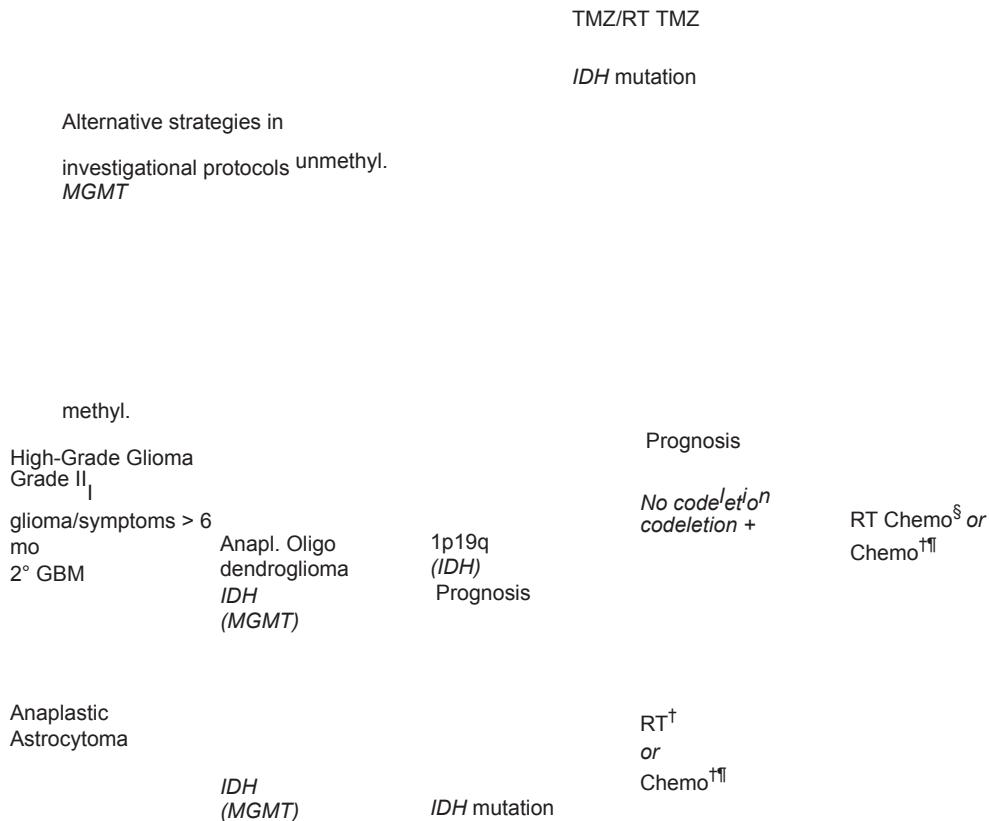


Figure 1. Treatment algorithm for high-grade glioma. GBM, glioblastoma; 1°, primary; 2°, secondary; MGMT, methyl-guanine methyltransferase gene pro mter methylation status; IDH, isocitrate dehydrogenase gene mutation; LOH 1p/19q, loss of heterozygosity of chromosomes 1 and 19; RT, radiotherapy; Chemo, chemotherapy with either PCV or temozolomide; PCV, procarabine, lomustine [CCNU], vincristine; TMZ, temozolomide. [†], RT or chemotherapy first, and at progression chemo or RT, respectively (according to NOA-04 study). , no randomised data for oligodendrogloma, only class III + V evidence. [§], subgroup analysis and long-term follow-up of RTOG and EORTC randomised studies demonstrated prolonged survival for patients treated with RT → PCV.

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chemotherapy appears largely restricted to this subgroup [16]. Feasibility of upfront testing and stratification by MGMT status has been demonstrated in large prospective trials, and alternative strategies for patients with unmethylated MGMT are proposed to patients as part of ongoing clinical trials. In the absence of effective better alternatives, TMZ/RT → TMZ remains the standard of care for the majority of GBM patients [II, B].

Owing to the overall inferior prognosis of elderly patients, shorter, simpler and less intensive treatment strategies have been investigated in frail or elderly patients approximately >65 years of age. Although hypo-fractionated RT (10 × 3.4 or 15 × 2.66 Gy) has been shown equivalent to standard fractionated irradiation with 30 fractions (60 Gy) in one trial [II, A] [32], the 6-week regimen was inferior compared with hypo-fractionated RT in patients >70 years in a subsequent larger randomised trial [19, 32], supporting the practice of administering RT as a short hypo fractionated course in elderly patients.

Primary chemotherapy versus radiotherapy has been compared in two randomised phase III trials reported in 2012 [19, 20]. Consistently, both trials have demonstrated a poor median overall survival (OS) of 7–9 months. MGMT promoter methylation was strongly predictive for a benefit from TMZ chemotherapy, suggesting that patients with a methylated MGMT are better treated with chemotherapy, while patients with an unmethylated MGMT should be managed with radiotherapy alone [II, A] [19, 20]. In the absence of information on the MGMT status, the appropriate treatment is hypo fractionated radiotherapy [II, A] [33]. A randomised, controlled trial (clinicaltrials.gov: NCT#00482677) investigating hypo fractionated RT ± concomitant and maintenance TMZ completed recruitment in 2013; first results are expected in late 2014.

Recent large phase III trials of novel treatment approaches failed to improve survival of patients with newly diagnosed GBM. Dose intensification of the adjuvant or maintenance TMZ therapy [36], the addition

of cilengitide [37] or the addition of bevacizumab [38, 39] did not translate into prolongation of OS. The clinical value of the observed prolonged PFS with bevacizumab remains controversial. The reported median OS from surgery in these clinical trials is ~16–18 months for both the control and experimental arms, and no substantial improvement over the results of the initial European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada TMZ trial [median 15 months, 95% confidence interval (CI) 13–17 months] was demonstrated.

anaplastic astrocytoma, oligoastrocytoma and oligodendrogloma (WHO grade III)

Anaplastic astrocytoma and oligoastrocytoma have a better prognosis compared with glioblastoma. Standard therapy consists of adjuvant radiotherapy up to 60 Gy after surgery. The value of concomitant and/or maintenance chemotherapy with TMZ has not been tested prospectively [V, D]. Long-term follow-up (10 years) of randomised clinical trials demonstrated prolonged survival with (neo)adjuvant PCV chemotherapy (procarbazine, lomustine [CCNU], vincristine) in newly diagnosed anaplastic astrocytoma and oligodendrogloma [40, 41], but benefit was mainly present in prognostically favourable molecular subgroups of patients (in particular co-deletion of 1p/19q) [II, B]. In a more recent randomised trial with follow-up data currently available up

to 4.5 years, time to failure of both chemotherapy and radiation was similar whether patients were treated initially with chemotherapy (and received RT at first progression) or were treated with initial RT (and received chemotherapy at progression) [I, A] [42]. An updated report is awaited. No difference of efficacy was apparent between PCV or TMZ chemotherapy [II, B].

diffuse glioma (WHO grade II)

Diffuse gliomas are low-grade tumours and comprise the histological subtypes of astrocytoma, oligoastrocytoma and oligodendrogloma. Although they have a protracted natural history of years or occasionally decades, and may not need immediate therapy, these tumours invariably recur and often transform into a higher histological grade.

The diagnosis is often made after an initial seizure is observed as a presenting symptom, or when imaging of the brain is carried out to investigate neurological deficits, changes in mood or personality. At that time, the tumour

may already have grown to a substantial size without causing evident neurological dysfunction, due to its slow growth over many years.

Radical surgery both for diagnostic and therapeutic purposes is the backbone of low-grade glioma management. It is assumed that, by resection of all visible tumour tissue, the risk of subsequent malignant transformation is substantially reduced [III, B].

In an exemplary randomised trial, investigators from the EORTC have demonstrated that an ‘expectative’ or cautious approach—delaying additional radiotherapy until symptoms prevail and the tumour has grown to >5–6 cm—will substantially delay or eliminate the need for irradiation in a significant number of patients [I, A] [43]. Adjuvant radiotherapy for a total dose of 50.4 Gy (28 × 1.8 Gy) is the accepted standard of care [I, A]. Two randomised trials investigated lower (45–50.4 Gy) versus higher dose (59.4–64.8 Gy) of irradiation; the lower dose was equivalent to the higher dose with less toxicity [44, 45]. Based on these trials, a number of negative prognostic factors were identified: tumour size >5–6 cm, tumours crossing the mid-line, absence of oligodendroglial histology, age >40 years and neurological deficits before surgery [46]. Three or more of these risk factors are considered an indication for adjuvant radiotherapy. A contemporary randomised trial compared adjuvant single-agent TMZ chemotherapy (without radiation) with standard radiotherapy. Preliminary results were presented at the American Society of Clinical Oncology meeting in 2013, and demonstrated that PFS analysis favours radiotherapy; however, follow-up is too early for firm conclusions and survival results are not yet mature [47]. Molecular characterisation of tumours may allow identification of subgroups of patients benefiting from one of the other treatment modalities, with 1p/19q co-deleted tumours having a similar PFS after TMZ chemotherapy compared with radiotherapy. The Radiation Therapy Oncology Group (RTOG) has conducted a randomised trial in a similar population exploring the efficacy of adjuvant PCV chemotherapy after radiotherapy. At the time of first presentation, the follow-up data were immature; thus, definitive conclusions are not yet possible [48].

recurrent disease

Some benefit of chemotherapy has been shown for patients with an adequate performance status who have not received prior

measurable anti-tumour efficacy of epidermal growth factor receptor (EGFR) inhibition by erlotinib or platelet-derived growth factor receptor inhibition by imatinib in an unselected patient population [II, C] [54, 55]. High response rates and a steroid-sparing effect have been observed with the administration of bevacizumab (\pm irinotecan); however, the effect is frequently short-lived and may be due exclusively to changes in vascular permeability; the effect on life expectancy remains unknown [III, C] [56, 57]. Randomised trials evaluating the pan-vascular endothelial growth factor receptor inhibitor cediranib or protein kinase C inhibitor enzastaurin failed to demonstrate improved outcome, and provide contemporary data on the limited but confirmed single-agent efficacy of lomustine (CCNU) [52, 53]. Applying alternating electric fields—tumour-treating fields (TTFs)—using a battery powered device connected to electrodes placed on the patient's scalp—was compared with physicians' choice of chemotherapy in a randomised trial in recurrent disease [58]. TTF failed to prolong survival compared with second-line chemotherapy [I, A].

There may be an indication for a re-operation [IV, C], in particular in patients where the recurrent tumour exerts an acute mass effect. However, there are no prospective data available on the impact of repeat surgery on OS. Retrospective analyses on selected patients did not identify surgery for recurrent disease as a significant prognostic factor for prolonged survival [59, 60]. Repeat surgery and implantation of carmustine-impregnated polymers may lead to marginal prolongation of survival compared with placebo, as demonstrated in a randomised trial conducted in the early 1990s [II, B] [61].

Re-irradiation is being considered increasingly for recurrent small tumours [IV, C], although there is considerable doubt about its benefit and the literature lacks prospective and comparative trials [62, 63]. The few limited size case series do not allow for any conclusion.

response evaluation

MRI is the preferred imaging method. Increased contrast enhancement and presumed tumour progression on imaging 4–12 weeks after the end of radiotherapy may be due to a reactive process following radiotherapy (pseudo-progression) [64, 65]. Early presumed progression after the end of radiotherapy should raise the possibility of pseudo-progression, and chemotherapy should be continued as planned with repeat imaging after 6–8 weeks. An incidence of >60% pseudo-progression has been reported among patients with early radiological progression after radiochemotherapy [66].

Response to chemotherapy is currently evaluated according to the 2D Response Assessment in Neuro-Oncology (RANO) criteria, in which in addition to contrast enhancement, tumour extension on T_2 - and fluid-attenuated inversion recovery

(FLAIR)-weighted MRI are evaluated [67]. Furthermore, an assessment of neurological function and

corticosteroid use is included. The recent introduction of anti-angiogenic and vascular modifying agents led to a reassessment of response criteria, in which, in addition to contrast enhancement, tumour extension on T_2 - and FLAIR-weighted MRI are to be evaluated [67]. In cases of doubtful differential diagnosis between tumour recurrence and treatment-induced unspecific changes (especially after multimodal therapy), magnetic resonance spectroscopy and positron-emission tomography investigation using an amino acid tracer (e.g. methionine, fluoro-ethyl-tyrosine) may be helpful [III, B] [68]. However, often both residual tumour and necrotic and inflammatory changes are present in the same lesion.

personalised medicine

Recent investigation of molecular markers, gene expression, whole genome sequencing and epigenetics has enabled identification of patient subgroups according to pathway activation, specific aberrations or pathognomonic molecular characteristics [69]. The clinical utility of IDH mutations, LOH 1p/19q and MGMT promoter methylation in prognostication and their predictive value and role in clinical decision-making have been discussed in the relevant subheadings above. ATRX mutations have been identified to be specific for astrocytic lineage. Other markers like EGFR overexpression and EGFR variant III (EGFRviii) mutation are characteristic for GBM that carry an inferior prognosis (reviewed in [70]). Targeting the EGFR with specific inhibitors and vaccination against EGFRviii are currently under clinical investigation [71]. Rare activating BRAF mutations can be identified in 3%–5% of GBM; whether the BRAF inhibitors are effective (alone or in combination) in this subgroup of tumours is subject of ongoing clinical research protocols. All planned investigational protocols are being designed for specific subgroups, selecting and enriching for specific molecular aberrations when targeting activated pathways.

follow-up and long-term implications

Follow-up consists of a clinical evaluation with particular attention to neurological function, seizures and corticosteroid use. Patients should be tapered off steroid use as early as possible. Venous thrombotic events occur frequently in patients with residual or recurrent tumours. Laboratory tests are not indicated unless the patient is receiving chemotherapy (blood counts), corticosteroids (glucose) or anti-epileptic drugs (blood count, liver function tests). MRI every 3–4 months is standard practice outside clinical trials, unless more frequent monitoring is clinically indicated.

note

A summary of recommendations is provided in Table 3. Levels of evidence and grades of recommendation have

been applied using the system shown in Table 4. Statements without grading were considered justified

standard clinical practice by the expert authors and the ESMO faculty.

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Table 3. Conclusions and recommendations

- Histological diagnosis is mandatory and should include sufficient tissue for molecular tumour characterisation
- Methyl-guanine methyl transferase (MGMT) promoter methylation, isocitrate dehydrogenase gene (IDH) mutations and co-deletions of 1p/19q are commonly determined depending on the histological and clinical context
- Surgery to the extent feasible is the first therapeutic intervention for all malignant glioma
- For glioblastoma, combined modality therapy with temozolomide (TMZ) and radiotherapy remains the standard of care. In elderly patients and a methylated MGMT promoter, exclusive TMZ chemotherapy may be considered, while (hypo-fractionated) radiotherapy is the treatment of choice for patients with an unmethylated gene promoter
- Anaplastic oligodendrogloma should receive radiotherapy and adjuvant chemotherapy, while no benefit has been demonstrated for adjuvant PCV chemotherapy (procarbazine, lomustine [CCNU], vincristine) in anaplastic astrocytoma
- In anaplastic glioma, treatment with adjuvant chemotherapy alone and irradiation only at the time of tumour progression is equivalent to the standard sequence of initial radiotherapy and salvage chemotherapy at the time of progression

Levels of evidence

- I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
- II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta analyses of such trials or of trials with demonstrated heterogeneity
- III Prospective cohort studies
- IV Retrospective cohort studies or case–control studies
- V Studies without control group, case reports, experts’ opinions

Grades of recommendation

- A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
- B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
- C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional

- D Moderate evidence against efficacy or for adverse outcome, generally not recommended
- E Strong evidence against efficacy or for adverse outcome, never recommended

^aBy permission of the Infectious Diseases Society of America [72].
conflict of interest

RS has reported that he is the president of EORTC, and has acted the principal investigator in pivotal studies investigating temozolomide, cilengitide or NovoTTF. He has received honoraria for advisory board participation from Roche/Genentech, and MSD/Merck & Co. He also received remuneration for participation in Advisory Boards organised by Roche, Amgen, AstraZeneca, Celgene and Sanofi. GP has reported research sponsored by Amgen, Teva, Roche, Boehringer Ingelheim and Sanofi. JCT has reported speaker’s honoraria and Advisory boards of Roche, MerckSereno and Medac. MV has reported that he is conducting research sponsored by Roche and by AbbVie. He is a member of the speaker’s bureau of MSD, and he has also received honoraria from Roche, AMGEN, Actelion, Merck AG, Celldex and AbbVie. MB has reported no potential conflicts of interest.

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