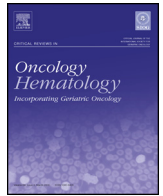




Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc



Childhood medulloblastoma

Maura Massimino^{a,*}, Veronica Biassoni^a, Lorenza Gandola^a, Maria Luisa Garrè^b,
Gemma Gatta^a, Felice Giangaspero^c, Geraldina Poggi^d, Stefan Rutkowski^e

^a Fondazione IRCCS–Istituto Nazionale dei Tumori, Milan Italy

^b IRCCS Giannina Gaslini, Genoa Italy

^c Università La Sapienza and Istituto Neuromed Pozzilli, Rome, Italy

^d Istituto Eugenio Medea, Bosisio Parini, Italy

^e University Medical Center Hamburg-Eppendorf, Department of Pediatric Hematology and Oncology, Hamburg, Germany

Contents

1. General information	00
1.1. Incidence	00
1.2. Survival	00
1.3. Risk factors	00
2. Pathology and biology	00
2.1. WNT medulloblastoma	00
2.2. SHH medulloblastoma	00
2.3. Group 3 medulloblastoma	00
2.4. Group 4 medulloblastoma	00
3. Diagnosis	00
4. Staging	00
5. Prognosis	00
6. Treatment	00
6.1. Surgery	00
6.2. Non-surgical treatment	00
6.2.1. Standard risk patients	00
6.2.2. High-risk group patients	00
6.2.3. Treatment for younger children	00
7. Late sequelae	00
7.1. Endocrine sequelae	00
7.2. GH deficiency (GHD)	00
7.3. Gonadal alterations	00
7.4. Thyroid nodules	00
7.5. Overweight/obesity, dyslipidemia, and metabolic syndrome	00
7.6. Neurocognitive outcome	00
7.7. Neurosensory late effects	00
7.8. Orthopaedic late-effects	00
7.9. Second tumours	00
8. Follow-up	00
8.1. Treatment at relapse	00
Acknowledgement	00
References	00

ARTICLE INFO

Article history:

Received 28 October 2015

Received in revised form 5 April 2016

Accepted 25 May 2016

ABSTRACT

Medulloblastoma accounts for 15–20% of childhood nervous system tumours. 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.

* Corresponding author at: IRCCS Foundation–Italian National Cancer Institute, Via Venezian, 1, 20133 Milan, Italy.

E-mail addresses: maura.massimino@istitutotumori.mi.it (M. Massimino), veronica.biassoni@istitutotumori.mi.it (V. Biassoni), lorenza.gandola@istitutotumori.mi.it (L. Gandola), gemma.gatta@istitutotumori.mi.it (G. Gatta), s.rutkowski@uke.de (S. Rutkowski).

<http://dx.doi.org/10.1016/j.critrevonc.2016.05.012>

1040-8428/© 2016 Elsevier Ireland Ltd. All rights reserved.

Keywords:

Medulloblastoma
Pediatric brain tumours
Prognosis
Target therapy
Molecular subgroups
Rehabilitation in brain tumours

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.

© 2016 Elsevier Ireland Ltd. All rights reserved.

1. General information

1.1. Incidence

Among all the childhood central nervous system (CNS) tumours, medulloblastoma and other neuroectodermal tumours (International Classification of Disease for Oncology – ICD-O codes 9470/3–9474/3) account for 25% of all CNS tumour cases in children (RARECAREnet, 2016), 15–20% represented by medulloblastoma. The European annual incidence rate was 6.8 per million children (age: 0–14 years) for the period 2000–2007, with high rates in Southern and Central Europe (RARECAREnet, 2016). Incidence was significantly higher in boys than in girls (about 40%). The annual incidence rate was higher in children between 1 and 9 years of age, slightly less than 8 per million; it was lower in infants (6 per million), and the lowest in 10–14-age children (4 per million) (Peris-Bonet et al., 2006). The incidence rate is higher in the age group 15–19 years (2.33/million/year) and decreases up to age 40, consistent with the embryonal origin of the tumour (Giordana et al., 1999). Rising incidence was recorded for medulloblastoma during the period 1978–1997, by 1.3% on average (Peris-Bonet et al., 2006). Incidence in North-America has been reported as 5.07 per million children (age: 0–19 years) (Kohler et al., 2011). For comparison, at the Children's Cancer Hospital Egypt between 2007 and 2013, on a total of 1114 diagnosis of brain tumours, embryonal tumours represented the 23.2% of the total, thus showing consistency with Europe and North America (Ezzat et al., 2016).

1.2. Survival

In European children with a medulloblastoma diagnosed in the period 2000–2007, 1-, 3- and 5 years survival figures were 81%, 63% and 56%. Infants had a worse prognosis: 5-year survival was 33%, slightly better for children aged 1–4 years (47%), while prognosis was significantly better (67%) for the age group 5–14 years (Kohler et al., 2011). Survival remained stable during the period 1999–2007 (Gatta et al., 2014), while it improved during the end of Nineties: the risk of dying reduced significantly by 30% (Gatta et al., 2009). Standard of care treatment for children older than 3–5 years entails surgical resection, craniospinal irradiation, and CT that has resulted in an overall cure rate, in clinical setting, of approximately 70–75% (Gatta et al., 2014; Gatta et al., 2009; Lannering et al., 2012). Outcome varied across European countries, suggesting difficulty to access to effective treatment and/or to reach timely and correct diagnosis. Actually, 5-year survival was better in Northern Europe (64%) and lowest in Eastern (53%) European countries (Gatta et al., 2014).

1.3. Risk factors

The peak of incidence of medulloblastoma/PNET (MB/PNET) occurs during childhood; therefore, factors operating very early

in life might play a key role. Birth weight has often been suggested to be a rough but easy indicator of prenatal exposures. Harder et al. conducted a systematic review on the association between birth weight and risk of specific histologic types of primary brain tumours. For medulloblastoma, high birth weight was significantly associated with increased risk (odds ratio–OR: 1.27; 95% CI 1.02–1.60) (Harder et al., 2008). Several studies have speculated on a potential infectious aetiology. A case-control study in England evaluated various perinatal factors and their impact on childhood brain tumour. The Authors found that the children of mothers who had a documented viral infection during pregnancy had 11-fold increased risk of malignant nervous system tumour (Fear et al., 2001). A further large population-based case control study investigated the patterns of day care and social contacts in the first year of life, as well as other markers of infectious exposure. Children reported to have had no social contact with other infants in the first year of life displayed an increased risk of developing a medulloblastoma (OR: 1.78; 95%CI 1.12–2.83) (Harding et al., 2009). However, other proxy markers of infectious exposure that were analysed (i.e., bedroom sharing, domestic exposure to school-age children, and birth order) did not support the hypothesis of a protective effect of infectious exposure. The role of diet, both as a risk and as a protective factor, has been investigated in several studies. Among the most extensively studied hypotheses is that maternal dietary intake of N-nitroso compounds (NOC) and NOC precursors during pregnancy increases brain tumour risk in offspring (Dietrich et al., 2005). Cured meats are a major source of dietary NOC. Maternal dietary was investigated in a large international collaborative case-control study on childhood brain tumours to evaluate associations between histology-specific risk and consumption of specific food groups during pregnancy. Foods generally associated with increased risk were cured meats, eggs/dairy, and oil products; foods generally associated with decreased risk were yellow-orange vegetables, fresh fish, and grains. However, cured meat was not associated with medulloblastoma. An increased risk was found between medulloblastoma and oil products (OR: 1.5; 95%CI 1.0–2.2 for 4th vs. 1st quartile; p trend=0.005) (Pogoda et al., 2009). A large Canadian study (Li et al., 2009) examined the contribution of maternal occupational exposure to extremely low frequency magnetic fields (ELF-MF) shortly before and during pregnancy on the incidence of childhood brain tumours. A significantly increased risk was observed for astroglial tumours as well as for all childhood brain tumours, but no association was specifically assessed for MB/PNET (MB/PNET). Several epidemiological investigations have attempted to evaluate the association between parental exposure to pesticide and childhood brain tumours, with the majority reporting positive associations (Baldwin and Preston-Martin, 2004). In a population-based case-control study, the association between the occurrence of brain cancer in children and parental exposure to pesticides in occupational and residential settings was evaluated. The authors observed little association with PNET for any of

the pesticide classes or exposure sources considered (Shim et al., 2009). A further study, that investigated the association between father's hobbies and MB/PNET (MB/PNET), found an increase risk of MB/PNET in children from the household exposures from hobbies, particularly pesticides. In multivariate analyses, a significant association was seen for lawn care with pesticides (during pregnancy: 1.6; 95% CI 1.0–2.5—after birth: OR: 1.8; 95% CI 1.2–2.8) (Rosso et al., 2008). Considering parental occupation, a European study found an elevated risk of PNET with parental exposure to polycyclic aromatic hydrocarbons (PAH) (OR: 2.0; 95% CI 1.0–4.0) and high maternal exposure to solvent (OR: 3.2; 95% CI 1.0–10.3) during the five-year period before birth (Cordier et al., 1997). Some genetic disorders (i.e., Gorlin Syndrome, Turcot syndrome, Li-Fraumeni syndrome) are cancer predisposition syndromes associated with an increased risk of medulloblastoma and will be further discussed (Villani et al., 2012).

2. Pathology and biology

The 2007 WHO classification of CNS tumours recognises the classic medulloblastoma and the following four variants:

- desmoplastic/nodular;
- medulloblastoma with extensive nodularity (MBEN);
- anaplastic;
- large cell (Giangaspero et al., 2007).

Of these variants, the anaplastic and large-cell medulloblastomas show a certain degree of overlapping and they have been grouped as large-cell/anaplastic (LC/A) medulloblastomas in several studies (Gilbertson and Ellison, 2008). The frequency of the combined LC/A form varies from 10% to 22% where anaplastic MB is diagnosed only in case of severe and diffuse (more than 50%) anaplasia. Nodular/desmoplastic medulloblastoma and MBEN comprise approximately 7% and 3% of all medulloblastomas, respectively. Classic tumours constitute the remainder (Giangaspero et al., 2007; Gilbertson and Ellison, 2008). Classic medulloblastoma is composed of densely packed cells with round-to-oval or carrot-shaped hyperchromatic nuclei surrounded by scanty cytoplasm. Desmoplastic/nodular medulloblastoma is a variant that contains nodular, reticulin-free zones, or “pale islands” which represent zones of neuronal maturation, exhibits a reduced nuclear cytoplasmic ratio, a fibrillary matrix, and uniform cells with a neurocytic appearance. These nodules are surrounded by densely packed mitotically active cells, which produce a dense intercellular reticulin-positive network of fibres. Medulloblastoma with extensive nodularity (MBEN) occurs in infants and it is associated with a good prognosis. It differs from the related nodular/desmoplastic variant by having an expanded lobular architecture, due to the fact that the reticulin-free zones become unusually elongated and rich in neuropil-like tissue. Such zones contain a population of small cells with round nuclei, which resemble the cells of a central neurocytoma and exhibit a streaming pattern. The internodular component is markedly reduced in some areas. The large cell medulloblastoma is composed of monomorphic cells with large, round, vesicular nuclei, prominent nucleoli and variably abundant eosinophilic cytoplasm. Groups or sheets of these “large cells” tend to mix with cells that have a different morphology characterised by marked nuclear pleomorphism and nuclear moulding. The latter phenotype has been labelled as “anaplastic” (Fig. 1).

Large cell and anaplastic medulloblastomas show considerable cytological overlap. Histological progression over time, from non-anaplastic to anaplastic types, has been described in several studies, and a transition can be even observed within a single tumour, as inferred from the presence of differing degrees of cytological atypia or anaplasia in one tumour (Eberhart et al., 2002a).

Clinical data strongly indicate a favourable prognosis for the nodular/desmoplastic medulloblastoma at least in some age- and risk groups, especially in young children (McManamy et al., 2007; Rutkowski et al., 2005). Moreover, comparing the outcome of classic and LC/A medulloblastomas, a significantly worse prognosis is evident for the LC/A variant (Eberhart et al., 2002a; McManamy et al., 2003; Massimino et al., 2013a).

The advent of molecular diagnostics has allowed medulloblastoma to be classified into distinct groups. According to the current international consensus, there are four molecular groups of medulloblastoma: wingless (WNT), sonic hedgehog (SHH), Group 3, and Group 4 (Fig. 2) (Kool et al., 2012; Taylor et al., 2012).

Differential diagnosis of a posterior fossa lesion includes as first the distinction from atypical teratoid/rhabdoid tumour (AT/RT). Histologically, small rhabdoid cells and large, pale, bland cells are common in AT/RTs. Gland-like structures are also seen. The tumour cells in AT/RT, but not those in medulloblastoma, are immunoreactive for vimentin, epithelial membrane antigen and smooth muscle actin. Molecular/cytogenetic analyses frequently have shown partial or complete deletions of chromosome 22 in both renal and extrarenal rhabdoid tumours, confirming their common origin. Mutations/deletions in the INI1 gene appear to be responsible for this lesion (Gessi et al., 2003; Judkins et al., 2004) (Fig. 2. Molecular subgroups of medulloblastoma. (Source: Taylor 2012 (Taylor et al., 2012)).

2.1. WNT medulloblastoma

This is the least common group of medulloblastoma, accounting for 11% of all cases (Kool et al., 2012). WNT medulloblastomas can occur at all ages, but predominantly affect older children, with a peak incidence in the age group 10–12 years. Gender ratio has a female preponderance, unlike the other subgroups. The tumours are typically located in the midline of the brain, occupying the IV ventricle and infiltrating the brain stem (Taylor et al., 2012; Gajjar and Robinson, 2014).

Histologically, the majority of WNT medulloblastoma are of the classic type; however, rare examples of WNT medulloblastoma with LC/A histology have been documented. WNT pathway tumours can be reliably identified by IHC expression of DKK1, Filamin-A, YAP-1, and beta-catenin (nuclear +/- cytoplasmic expression) (Gajjar and Robinson, 2014; Ellison et al., 2011). Metastatic diffusion is much lower, compared to other groups. Prognosis in this group is the best of all four groups, with survival rates around 95–100%. The reasons for improved survival in this group is not known, but could be related to increased sensitivity to RT (Salaroli et al., 2015). In the WNT group, over 75% of tumours harbour a point mutation in exon 3 of the CTNNB1 gene (encoding beta-catenin), leading to hyper-activation of the WNT pathway by rendering beta-catenin resistant to degradation and causing nuclear accumulation of the protein with increased transcription of genes involved in cellular proliferation including cyclin D1 and MYC (Gilbertson, 2004). Cytogenetically, WNT pathway tumours are characterised by deletion of one copy of chromosome 6 (monosomy 6) in the majority of patients (42 of 53 tumours; 79%) (Shih et al., 2014). Other than monosomy 6, the genome of WNT medulloblastoma is relatively silent and associated with only very few regions of chromosomal gain and/or loss across the genome (Gilbertson, 2004).

Copy number variation (CNV) and/or single nucleotide variants (SNV) include (in addition to monosomy 6) mutations in the DEAD-box RNA helicase gene that enhances cellular proliferation by increasing the trans activating capacity of beta-catenin, SMARCB4 (26%), TP53 mutation (16% of cases, without a corresponding germline mutation; it does not seem to affect the excellent prognosis of this group), tetraploidy (14% of tumours; it

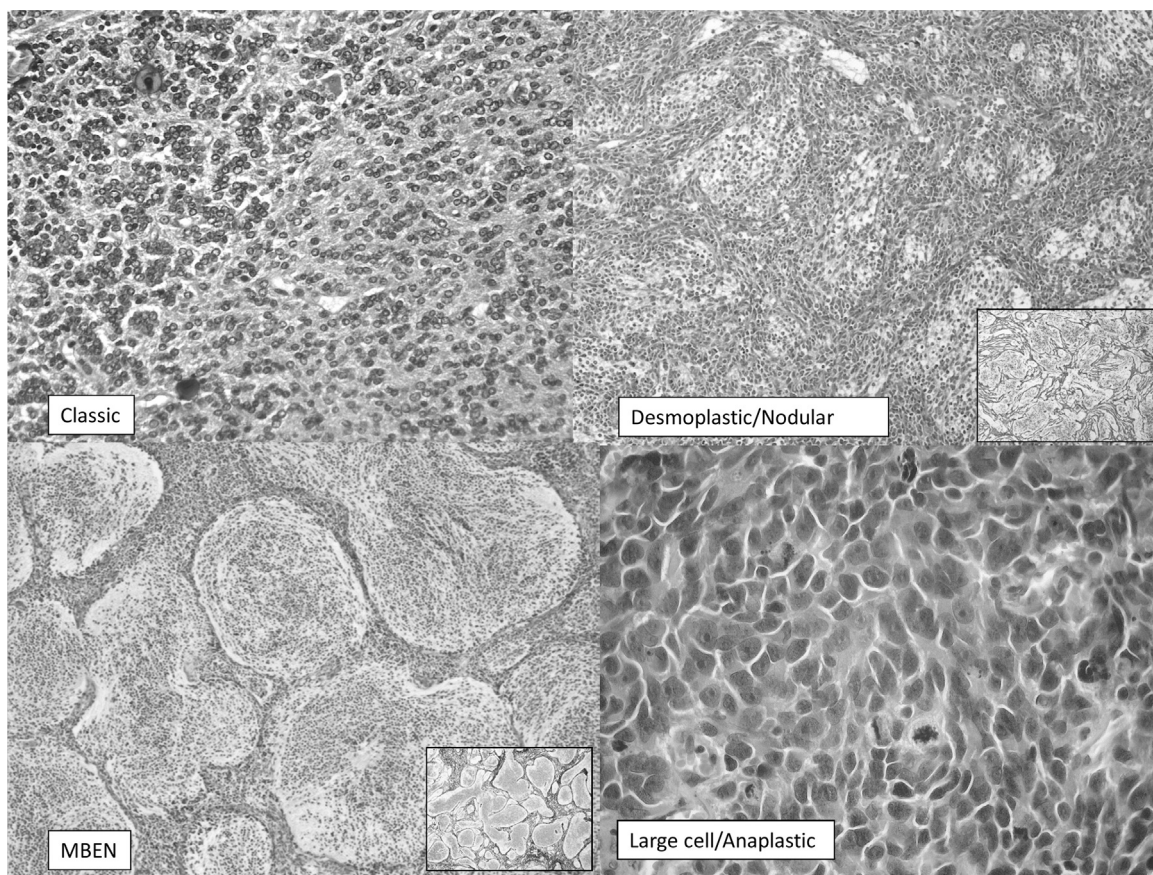


Fig. 1. Histologic subtypes of medulloblastoma.

might be an early event in tumorigenesis), and MLL2 mutations (2%) (Northcott et al., 2012; Jones et al., 2012). Assessment of WNT subgroup patients in the HIT-SIOP-PNET4 cohort revealed significant new insights into their clinical behaviour with relapses observed at higher frequency in patients 16.0 years at diagnosis (Clifford et al., 2015–17), consistent with the bi-modal age distribution and worse prognosis reported for adults compared to children within WNT medulloblastoma in retrospective series (Kool et al., 2012; Clifford et al., 2015–17; Korshunov et al., 2010).

2.2. SHH medulloblastoma

The SHH pathway plays a key role in normal cerebellar development where it induces proliferation of neuronal precursor cells in the developing cerebellum and other tissues. The SHH ligand is normally secreted by Purkinje cells and promotes formation of the external germinal layer from granule cell precursor (GCP) cells (McManamy et al., 2007). Paracrine signalling from SHH or constitutional activation due to PTCH1 mutations results in dissociation of the serpentine G-protein coupled receptor SMO from PTCH, which then translocates into the tip of the primary cilium and releases GLI2 from its natural repressor, suppressor of fused homolog (SUFU). GLI2 then migrates into the nucleus and transcriptionally activates genes involved in cellular proliferation of GCP of the cerebellum leading to tumour formation (Archer et al., 2012). SHH subgroup accounts for about 30% of all medulloblastomas and has a bimodal age distribution, occurring mostly in infants (<3 years) and adults (>16 years), and less frequently in patients who are 3–16 years old (Taylor et al., 2012; Gibson et al., 2010). The gender ratio is about 1:1, although there is a slight male predominance among infants (Gajjar and Robinson, 2014).

SHH medulloblastoma frequently occur in a hemispheric location in the cerebellum (Fig. 3), although some tumours arise in the midline vermis (Jones et al., 2012). Histology is typically of the nodular/desmoplastic type with MBEN being exclusively classified into this group. The others are either of classic or LC/A histology. SHH medulloblastomas can be identified readily using tumour IHC expression for GAB1, SFRP, and GLI1 protein (Ellison et al., 2011). Metastatic disease at diagnosis occurs rarely (Taylor et al., 2012). As previously mentioned, about 3–5% of patients with Gorlin Syndrome and germline PTCH1 mutation exclusively develop nodular/desmoplastic medulloblastoma.

PTCH1 mutations have been reported in 36–54% of SHH medulloblastoma, making it the most prevalent mutation of this group (Kool et al., 2014). The identification of somatic mutations of PTCH1 in non-Gorlin patients further established the link between medulloblastoma and SHH signalling, including mutations in SMO and SUFU, amplifications of SHH, GLI2, and MYCN genes. Amplifications of MYC or MYCN have previously been associated with large-cell/anaplastic histology and poor patient survival. Moreover, tumours with amplification of either MYC or MYCN and tumours harboring gain of 6q comprise subgroups with a particularly poor prognosis (Eberhart et al., 2002b). In a recent large-scale genomic study of SHH medulloblastoma, PTCH1 mutation occurred at a roughly equal frequency in infants (36%), children (42%), and adults (54%). SUFU mutations were found almost exclusively in infants, and SMO mutations were enriched in tumours occurring in adults (Kool et al., 2014).

In older children, SHH medulloblastomas have a broader molecular heterogeneity, with amplification of SHH, GLI2, and MYCN. Zhukova et al. reported TP53 mutations enriched in tumours of older children with SHH medulloblastoma (21% of cases), and

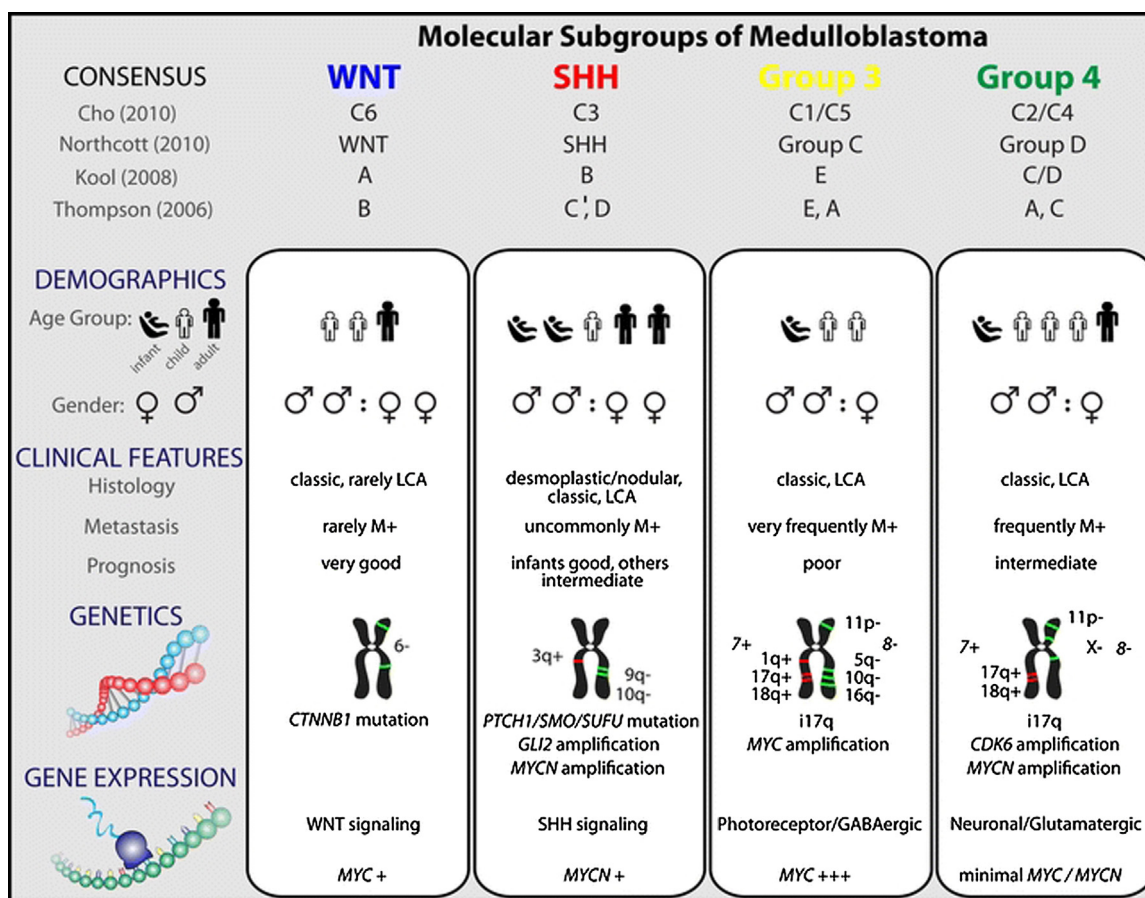


Fig. 2. Medulloblastoma molecular subgroups.

over 50% were found to have germline mutations and, hence, Li-Fraumeni that conferred patients a significantly worse prognosis (Zhukova et al., 2013). Copy number aberrations include amplifications of protein phosphatase ID (PPM1D, chromosome 17q23.2), IGF1R, IRS2, PIK3C2G, PIK3C2B, and YAP-1 along with PTEN deletion on chromosome 10q23.31 and mutations in DDX3X (11%) (Northcott et al., 2012). Tetraploidy is present in about 29% of samples and it is associated with p53 mutations and chromothripsis (Jones et al., 2012).

Patients in SHH group rarely have a disseminated tumour at diagnosis and as a whole have an intermediate prognosis, with a 5-year overall survival of approximately 75% when treated with standard therapy (Taylor et al., 2012). Recent studies have however shown that GLI2 amplification, chromosome 14 loss, 10q deletion, MYCN amplification, anaplasia, and/or metastatic disease at diagnosis identify further subgroups in SHH medulloblastoma patients conferring them the worst prognosis (Min et al., 2013).

2.3. Group 3 medulloblastoma

Group 3 medulloblastoma accounts for about 25–28% of cases and it is exclusively found in children, with a male predominance, and has a high incidence of metastatic disease at diagnosis and frequently LC/A histology (Northcott et al., 2012).

No germline mutations have been described to predispose children to group 3 medulloblastoma and little is known about its molecular pathogenesis. While IHC expression for Natriuretic Peptide Receptor 3 (NPR3) has been reported to confirm this subgroup, others have questioned the validity of this marker, which should not be routinely used for clinical purposes until further validation

in prospective cohorts of newly diagnosed patients (Taylor et al., 2012; Min et al., 2013).

Focal high-level amplification of MYC and OTX-2 proto-oncogenes are observed in approximately 12–16% and 7% of these tumours, respectively, and most have aberrant MYC expression (Northcott et al., 2012). The genome in group 3 medulloblastoma is highly unstable and frequent gains of 1q, 7, and 17q (i17q) are observed along with 10q, 11, 16q, and 17p deletions (Northcott et al., 2012). Tetraploidy is seen in 54% of group 3 tumours and probably occurs as an early event in tumorigenesis (Jones et al., 2012). Chromothripsis (in the absence of p53 mutations) frequently occurs in this malignancy, resulting in bizarre chromosomal rearrangements or fusions in an attempt at ineffective DNA repair. There also appears to be up regulation of TGF- β signalling due to single copy number aberration of the genes in this signalling pathway and interaction with downstream targets that include OTX-2 (Northcott et al., 2012). This subgroup is associated with the worst prognosis amongst all four molecular groups of medulloblastoma with survival of <50%, with no survivors past 120 months of follow-up in evaluation of retrospective cohorts (Kool et al., 2012). In a multivariate analysis, Shih et al. showed that the presence of i17q, MYC amplification, and presence of metastatic disease confer the worst prognosis in this group, and those without these markers fare relatively better (Shih et al., 2014). In testing novel agents in this pre-clinical model of group 3 medulloblastoma, Pei et al. have shown that these tumours are sensitive to PI3 kinase and mTOR inhibitors (Pei et al., 2012). Similarly, the group at St. Jude Children's Hospital, using a high-throughput cell-based assay to treat Group 3 medulloblastoma neurospheres, identified pemetrexed and gemcitabine to selectively inhibit proliferation of this tumour type both

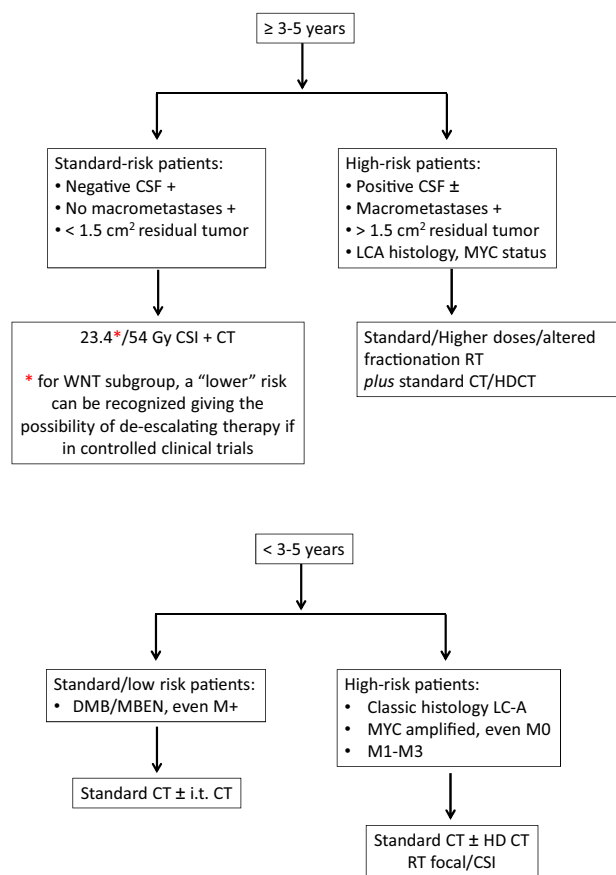


Fig. 3. Classification of patients by risk.

in vitro and in vivo and in combination with standard therapies; it might be a promising treatment for children with group 3 medulloblastoma (Morfouace et al., 2014).

2.4. Group 4 medulloblastoma

Group 4 is the most common molecular group of medulloblastoma, accounting for about 35%. This tumour type can affect all ages, but it is rare in infants. There is a significant male predominance (3:1) (Northcott et al., 2012). Histologically, the vast majority of Group 4 medulloblastoma are of classic histology, although cases of LC/A have been observed. KCNA1 has been suggested as an IHC marker for Group 4, but it is awaiting validation (Ellison et al., 2011). Patients in this group have an intermediate prognosis with conventional cytotoxic therapy. Shih et al. have identified that loss of chromosome 11 and presence of i17q in a subset of patients with group 4 medulloblastoma confer an excellent prognosis irrespective of metastatic disease (Shih et al., 2014). The underlying biology of Group 4 medulloblastoma is not well understood. Similarly to group 3 tumours, tetraploidy occurs as an early change (40% of cases) (Jones et al., 2012). Additionally, genes MYCN and CDK6 (cyclin dependent kinase 6) are commonly amplified. Isochromosome 17q occurs in 80% of cases, as does 17p deletion (Skowron et al., 2015). Most group 4 tumours in females lose one copy of the X chromosome, which raises the possibility of the existence of one or more tumour suppressor genes on this chromosome (Jones et al., 2012). Additionally, chromatin-remodelling genes are mutated in this group and include KDM6A (that codes for a H3K27 methylase and located on chromosome Xp11.3), ZMYM3, and CHD7. These mutations, along with overexpression of enhancer of Zeste homologue 2 (EZH2), keep neural stem cells in an undifferentiated state

and might be sustaining tumorigenesis. Table 1 describes main clinical and genomic characteristics of medulloblastoma subgroups.

3. Diagnosis

The radiological differential diagnosis of tumours located in the posterior fossa includes medulloblastoma, cerebellar astrocytoma, ependymoma, brainstem glioma, and atypical teratoid/rhabdoid tumour. Computed tomography (CT) is sometimes the first-line neuroimaging modality for patients with posterior fossa tumours because of its availability in an emergency setting. A typical feature of medulloblastoma revealed with CT is a midline, homogeneous, contrast-enhancing cerebellar vermian mass. Magnetic resonance imaging (MRI) is, however, a mandatory diagnostic and follow-on imaging, that should be carried out before tumour surgery. MRI features that are typical of medulloblastoma include a heterogeneous hypointense mass on T1-weighted imaging. In contrast to other CNS tumours that show T2-weighted hyperintensity compared with grey matter, medulloblastomas is intermediate between grey and white matter, reflecting a high cellular density. Contrast enhancement of medulloblastomas is usually heterogeneous. Spinal metastases, which occur in up to 40% of patients, are most commonly seen in the lumbosacral and thoracic areas and are best seen on post-contrast T1-weighted images. In doubtful cases, they should be confirmed or excluded by axial slices. It is therefore imperative to have an MRI of the spine before starting any adjuvant treatment. Thin sliced T2 can be useful to appreciate small nodules in non-enhancing leptomeningeal disease spread that could be underestimated with T1 plus contrast sequence. Whole CNS imaging should be repeated before defined phases of postoperative treatment (Buhning et al., 2002) as a standard procedure.

Medulloblastoma can be disseminated at diagnosis, and sometimes occurs in the brain with a particular predisposition for subependymal areas of the ventricles. Other imaging modalities, such as magnetic resonance spectroscopy (MRS), PET, and single photon emission computed tomography (SPECT), can be helpful to distinguish tumour recurrence from post-therapy necrosis. A recent issue coming to the available literature is the possibility to distinguish histological subtypes and molecular subgroups on the basis of different MRI features. The apparent diffusion coefficient (ADC) value is reported as lower in classic medulloblastoma than in LC/A variety, and the presence of focal cysts correlate with the classic and desmoplastic subtypes. Leptomeningeal diffusion suggests LC/A subtype as well as tumour necrosis (Yeom et al., 2013). On the molecular ground, tumour location and enhancement pattern have been described as significant predictors of medulloblastoma subgroups: WNT tumours can be localised mostly in the cerebellar peduncle and cerebellar-pontine angle, SHH tumours arise in the cerebellar hemispheres and group 3 and 4 tumours predominate within the midline fourth ventricle. Moreover, midline group 4 ones present with minimal or no enhancement (Perreault et al., 2014). These imaging modalities and indications might have substantial implications for the future directions of research into medulloblastoma. However, these evaluations are to be considered still investigational.

4. Staging

Staging and subsequent risk stratification are crucial in the management of medulloblastoma. Current staging classification requires MRI of the brain and entire spine with and without gadolinium and analysis of the cerebro-spinal-fluid (CSF). CSF from the lumbar region is preferred, because it is a more sensitive medium than ventricular fluid for detecting disseminated disease. CSF should be obtained postoperatively from the lumbar region 2 weeks after surgery to avoid a false-positive cytology after the

Table 1
Clinical and genomic characteristics of subgroups.

	WNT	SHH	GROUP 3	GROUP 4
HISTOLOGY	Classic, Rarely LCA	Desmoplastic, Classic, LCA	Classic, LCA	Classic, LCA
METASTATIC RATE	Low	Low	High	High
PROGNOSIS	Excellent	Intermediate	Poor	Intermediate
Somatic Copy Number Alterations	–	MYCN (12%)newline GLI2 (8%)	MYC (17%) PVT1 (12%) OTX2 (8%) SMARCA4 (11%) MLL2 (4%)	SNCAIP (10%) MYCN (6%) CDK6 (5%) KDM6A (13%) MLL (5%)
Single-Nucleotide Variants	CTNNB1 (91%) DDX3X (50%) SMARCA4 (26%) MLL2 (13%) TP53 (13%)	TERT (60%) PTCH1 (46%) SUFU (24%) MLL2 (16%) SMQ (14%) TP53 (13%)		
BROAD EVENTS	6 Loss	3q Gain 9q, 10q, 14q Loss	1q, 7, 17q, 18q Gain 8, 10q, 11, 16p, 17p Loss	7, 17q, 18q Gain 8,11p, X Loss
EXPRESSION	WNT Signaling	SHH Signaling	MYC/Retinal Signature	Neuronal Signature
RECURRENCE	–	Local	Metastatic	Metastatic

initial resection (Gajjar et al., 1999). Contraindications for lumbar puncture (e.g., increased intracranial pressure) must be considered cautiously. Assessment of the CSF for disseminated disease is crucial, because up to 10% of adults and 30% of children have evidence of disseminated disease at presentation (Koeller and Rushing, 2003).

Patients are generally divided into risk-stratified schemes on the basis of their age, the extent of residual disease, dissemination, LC/A-MB, MYC and WNT status (Fig. 3). Residual disease has been classified as $>1.5 \text{ cm}^2$ on the axial plan as determined by early (within 24–72 h) post-operative MRI (Packer et al., 2003a). The type of metastatic extension is determined according to Chang's classification for metastases (Table 2) (Chang et al., 1969).

Sixty to 70% of patients older than 3 years are assigned to the average-risk group. High-risk patients include people in the disseminated category, patients who have less than a gross or near-total resection, which is arbitrarily defined as 1.5 cm^2 of post-operative residual disease (Fig. 4), patients having tumours with MYC amplification and those having a LC/A histologic subtype.

Tumour staging will be probably implemented in forthcoming trials through integration with new biological findings after evaluation of retrospective or prospective series and correlated with outcome (Northcott et al., 2012; Jones et al., 2012)

5. Prognosis

Today, current treatment protocols that include surgery, craniospinal irradiation, and CT have achieved 5-year overall survival rates over 70% for standard-risk patients (Gatta et al., 2009).

Until a few years ago, metastatic medulloblastoma series reported dismal results with 5-year survival around 30–50% (Evans et al., 1990). Nowadays, intensified CT regimens (myeloablative schedules with hematopoietic support of peripheral harvested stem cells), non-conventional RT schedules and concomitant radiation and radiosensitizers schedules seem to have improved prognosis – with 5-year survival rates around 70% – that will need to be confirmed in further trials (Gajjar et al., 2006; Gandola et al., 2009; Dufour et al., 2014; Jakacki et al., 2012 Jul 20).

Similar considerations can be applied to younger children (under 3 or 4–5 years of age at diagnosis, according to national policies) who have traditionally been treated with risk- and age-adapted RT – frequently reducing total craniospinal doses – and prolonged CT schedules with the aim of reducing late sequelae, especially those related to radiation treatment, and therefore reducing the risk of relapse and intensive re-treatment for around 50% of patients (Duffner et al., 1993; Grill et al., 2005). The most recent German experience, using systemic CT schedule combined with intraventricular methotrexate, has resulted in a 5-year

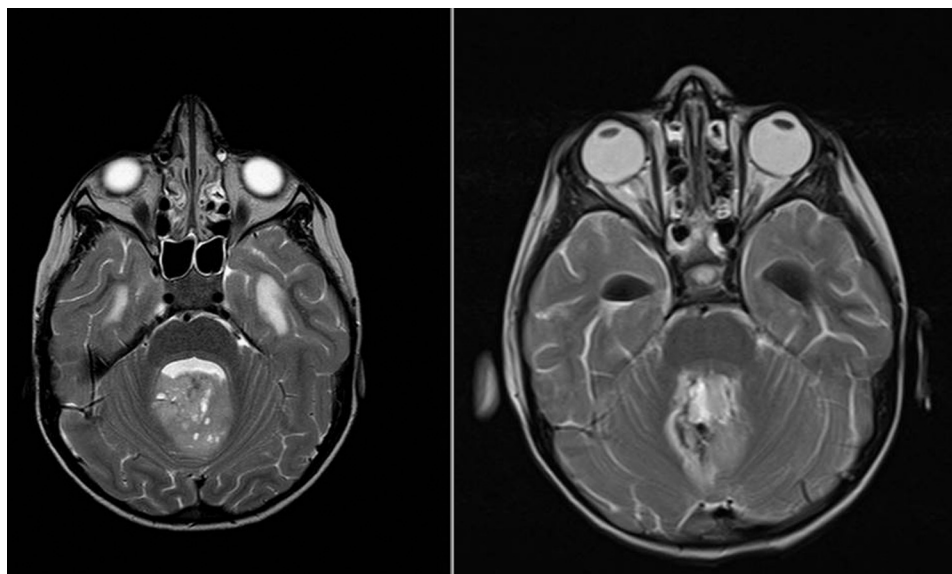


Fig. 4. A sub-total resection: on the left the basal MRI (Flair sequence).

Table 2
Chang classification for metastases.

M0	No gross nodular or laminar subarachnoid or haematogenous metastasis
M1	microscopic tumours cells found in CSF
M2	Gross nodular or laminar seeding in the cerebellum, cerebral subarachnoid space, or in the third or fourth ventricles
M3	Gross nodular or laminar seeding in the spinal subarachnoid space
M4	Extra-neuraxial metastasis

progression free survival (PFS) of 83% (Rutkowski et al., 2005), thus demonstrating that a tailored use of drugs is able to replace RT, at least in some sub-groups of patients. It has become increasingly recognized over the past decade that the desmoplastic/nodular variants of medulloblastoma are more common than had been previously appreciated in young children with medulloblastoma, and that this pathologic subtype is predictive of a superior survival rate (Leary et al., 2011; von Bueren et al., 2011), therefore common future cooperative strategies will develop chemotherapy only strategies with the aim of lowering sequelae.

6. Treatment

Current and currently planned clinical trials will aim at both improving prognosis and reducing treatment sequelae by:

1. evaluating the feasibility of reducing both the dose of craniospinal irradiation and the volume of the posterior fossa RT boost by the new knowledge on biological stratification factors in standard-risk patients;
2. determining whether intensification of CT or irradiation can improve outcome in patients with newly-defined high-risk disease.
3. Introducing of available targeted therapies in suitable constellations.

Future patients will be enrolled in clinical trials that will identify the risk based on both clinical factors and molecular grouping of this tumour in real time, allowing for de-escalation of therapy for patients with low or average-risk disease and treatment intensification for patients with high-risk tumours.

6.1. Surgery

Surgical resection is a fundamental part of treatment. Depending on the location and dimensions of the tumour, an external ventricular shunt or third ventriculostomy might be needed as emergency treatment, before tumour resection, to decrease intracranial pressure secondary to fluid circulation obstruction at the foramina of Lukscha, foramina of Magendie, or the aqueduct of Sylvius. About 20–30% of patients will require a permanent ventriculo-peritoneal shunt consequent to scarring of the cerebrospinal fluid pathways (Papo et al., 1982). The close relationship of medulloblastoma to the fourth ventricle and sometimes brainstem is a risk for morbidity, but expert paediatric neurosurgeons are frequently able to remove the tumour gross totally without creating major morbidity (Albright et al., 2000). Apart from infections and mechanical complications, such as fluid leak and pseudomeningocele, direct neurosurgical manipulation can cause posterior fossa mutism syndrome (Robertson et al., 2006). This is characterised by mutism developing 48–72 h after resection, and it is associated with severe cerebellar deficits such as dysmetria, hypotonia, paresis, and mood depression, which can last several months. It is probably secondary to disruption of reticular substance pathways. The degree of surgical resection is best assessed on a post-operative MRI brain (within 48 h after surgery). However, a small amount of tumour, visible to the operating surgeon's eyes, is below the limits of resolution of current scanners and can be left behind, and a careful discussion with the neurosurgeon and a review of the operative

report is important in treatment planning. Patients with a reduction of postoperative residual tumour through second surgery to less than or equal to 1.5 cm² are eligible for standard risk protocols providing this approach is discussed and afforded in due time, generally within two weeks after first surgery. In the light of the important appreciation of molecular risk categories in subgrouping, the risk correlated to incomplete resection compete with risk biological issues and a near total resection, if less risky, can be acceptable instead of a gross total resection.

6.2. Non-surgical treatment

6.2.1. Standard risk patients

After surgical resection, the mainstay for patients older than 3–5 years at diagnosis is “reduced-dose” craniospinal irradiation (CSI) with a total dose of 23.4 Gy plus a localised boost to the posterior fossa up to a total dose of 54–55.8 Gy. The clinical target volume (CTV) for CSI includes the whole brain and spinal cord including meninges down to the thecal sac at L5 or S3 level. Inadequate coverage of the cribriform plate region can result in sub-frontal relapse following CSI; hence treatment planning should adequately include this region without causing undue radiation exposure to the eye globes and a subsequent risk of cataracts (Packer et al., 2006).

In recent years, CT and MRI scans have been increasingly used to plan the target volumes for irradiation. The planning axial CT scan image is obtained through the treatment area of the brain with the patient in a customised immobilization device. Reduced doses craniospinal irradiation is usually combined with weekly concurrent single-drug (vincristine) and followed by a multidrug regimen that can be cisplatin, vincristine and lomustine, or cisplatin, vincristine and cyclophosphamide (Packer, 1990). Five-year event-free survival (EFS) based on this regimen is over 80%. A regimen with hyperfractionated radiotherapy (36 Gy in 36 fractions) to the craniospinal axis, a boost with conformal therapy restricted to the tumour bed (to a total dose of 68 Gy in 68 fractions), and no chemotherapy has been also adopted in the context of a multicentric national ground with, importantly, online quality control that granted early radiotherapy plan correction when needed with 3-year EFS of 80% (Carrie et al., 2005).

The HIT-SIOP PNET4 trial, conducted and closed in Europe (Gatta et al., 2009), compared conformal conventionally fractionated craniospinal RT at a dose of 23.4 Gy plus boost with hyperfractionated craniospinal irradiation (2 × 1 Gy/d) at a dose of 36 Gy plus boost, followed by the same CT schedule with 8 courses of vincristine (1.5 mg/m² for 3 doses), cisplatin (70 mg/m²) and lomustine (75 mg/m²). The aims of this randomised trial were to compare PFS and late effects after the two different radiation schedules. Hyperfractionated radiation is a technique that, at least theoretically, can achieve increased tumour cell kill with equal effects on critical normal tissues, or reduce normal tissue effects without reduction of tumour cell kill.

In all, 340 children aged 4–21 years from 122 European centres were post-operatively staged and randomly assigned to one of the two arms. After a median follow-up of 4.8 years (range 0.1–8.3 years), survival rates were not significantly different between the two treatment arms:

- 5-year event-free-survival (EFS) was $77\% \pm 4\%$ in the conventional radiation group and $78\% \pm 4\%$ in the hyperfractionated RT group;
- corresponding 5-year overall survival (OS) was $87\% \pm 3\%$ and $85\% \pm 3\%$, respectively.

A postoperative residual tumour of more than 1.5 cm² was the strongest negative prognostic factor. EFS of children with all reference assessments and no large residual tumour was $82\% \pm 2\%$ at 5 years.

Patients with a delay of more than 7 weeks from the beginning of RT had a worse prognosis.

Severe hearing loss was not significantly different for the two treatment arms at follow-up.

A further reduction of craniospinal irradiation dose under 23.4 Gy of posterior fossa boost dimensions is currently under evaluation in a randomised Children's Oncology Group (COG) study, and is also studied in a subset of standard-risk patients with WNT subgroup disease under 16 years of age who will be treated in the recently open European SIO-PNET 5 clinical trial.

6.2.2. High-risk group patients

As already mentioned in the «Staging» section, patients are stratified for therapy into standard and high-risk groups according to their clinical presentation, depending on the presence of metastases alone (M1–M4) or with postoperative residual disease >1.5 cm², but also biological factors like LC/A-histology or MYC-amplification will be considered in upcoming trials. The prognosis for high-risk medulloblastoma is still unsatisfactory. Ever since the 1980's, when medulloblastoma, whether high-risk or not, has been treated with a protocol including radiation therapy and CT (vincristine and CCNU), patients had a better prognosis if they received CT (Evans et al., 1990; Tait et al., 1990). CT is therefore part of adjuvant treatment in this group of patients, but optimal timing and schedule are not yet established.

We will illustrate in the following lines the concept of each strategy adopted since the Eighties and the survival: conventional RT and standard doses CT in a pre-RT or maintenance schedule, high-dose CT with conventional RT, higher doses of RT with high-dose chemotherapy, altered fractionation of RT and CT, radiosensitizer CT. A single centre study considering the use of RT followed by vincristine, cisplatin, and CCNU in high-risk patients reported a survival rate of around 85% (Packer et al., 1988). These results were much better than the SFOP (French Society of Paediatric Oncology) study, which treated high-risk patients with the “eight-drugs-in-one-day” CT regimen, followed by two cycles of high-dose MTX, RT and then further “eight in one” CT (Gentet et al., 1995). The subsequent French national study confirmed the rate of response to the “sandwich” CT, but was without any significant improvement in either M1 or M2/M3 patients, who achieved a 5-year EFS of 58.8% and 43.1%, respectively (Verlooy et al., 2006). The COG921 randomised phase III trial, open from 1986 to 1992, also proposed an “eight-in-one” CT regimen before and after RT. The 83 metastatic patients had a significantly lower PFS than the standard-risk patients (57% M1; 40% M2; 78% NED/M0, $p = 0.0006$) (Zeltzer et al., 1999). In the randomised prospective multi-centre trial HIT '91, post-operative neoadjuvant CT (ifosfamide, etoposide, IV high-dose methotrexate, cisplatin and cytarabine given in two cycles) followed by craniospinal RT was compared to maintenance CT after immediate postoperative RT (“Philadelphia protocol”). The 3-year PFS for all randomised patients was 65% for M1 patients and 30% for M2–M3 patients, thus achieving a statistically significant difference (Kortmann et al., 2000). The European phase III clinical trial SIO-PNET/UKCCSG PNET-3 ascertained the feasibility of treating high-risk medulloblastoma with neoadjuvant CT (vincristine, cisplatin, etoposide, and cyclophosphamide), followed by a standard CSI dose with a posterior fossa boost and/or a boost to metastases. The

outcome was rather unsatisfactory in metastatic patients in comparison with earlier multi-institutional series, obtaining a 5-year PFS of less than 40% (Taylor et al., 2005).

More recent studies have produced encouraging results with high-dose CT and autologous stem cell transplantation with standard RT. Strother et al. enrolled 19 patients with metastases for treatment with topotecan, followed by CSI and four cycles of high-dose cyclophosphamide with cisplatin and vincristine, followed by CPC reinfusion. The PFS 2 years after starting the therapy was $73.7\% \pm 10.5\%$ (Strother et al., 2001). This experience was expanded, treating a total of 42 metastatic patients, and obtaining a 5-year EFS of 66% (Gajjar et al., 2006). A preliminary study was conducted on 9 patients with supratentorial primitive neuroectodermal tumours and metastatic medulloblastoma treated with high-dose cyclophosphamide with cisplatin, vincristine, etoposide and high-dose MTX for 2–3 cycles before RT. The results were interesting: 7/9 patients were tumour-free after a median follow-up of 27 months (Dhodapkar et al., 2002). In a more recent trial, open from 1997 to 2003, 21 young patients with high-risk or disseminated medulloblastoma were enrolled for evaluation of their response rate to an intensified induction CT regimen and single myeloablative CT cycle with autologous stem-cell rescue. This was followed by RT for patients more than six years of age, or with evidence of residual disease on completion of the induction CT if under 6 years old. The 3-year EFS and OS were 49% and 60%, respectively (Chi et al., 2004). Dufour recently published a study aimed to assess the feasibility and effectiveness of tandem high-dose CT with stem cell support followed by conventional craniospinal RT in the treatment of children older than 5 years of age with high-risk medulloblastoma (19 metastatic) or supratentorial PNET. At a median follow-up of nearly 4 years for children with metastatic MB, the EFS and OS rate at 3 years were 78% (95%CI 55–91) and 83% (95%CI 59–94), respectively, EFS and OS rate at 5 years were 72% (95%CI 48–87), and 83% (95%CI 59–94), respectively, thus supporting the statement that this approach could improve results (Dufour et al., 2014).

Gandola et al. (Gandola et al., 2009) have reported on 33 consecutive patients, treated in an almost monoinstitutional setting, receiving post-operative methotrexate (8 g/m²) plus vincristine, etoposide (2.4 g/m²), cyclophosphamide (4 g/m²), and carboplatin (0.8 g/m²) in a 2-month schedule. Hyperfractionated accelerated RT (HART) was then delivered at a total dose to the neuraxis of 39 Gy (1.3 Gy/fraction, 2 fractions/day) with a posterior fossa boost up to 60 Gy (1.5 Gy/fraction, 2 fractions/day). In cases of persistent disseminated disease before HART, patients were consolidated with 2 courses of myeloablative CT and circulating progenitor cell rescue. Otherwise, they received a maintenance CT with vincristine and lomustine for one year. With a median follow-up of 82 months, the 5-year EFS, PFS and OS were 70%, 72% and 73%, respectively. Jakacki et al. reported on the outcome, in the subset of patients with metastatic medulloblastoma, of a Children's Oncology Group (COG) study. After surgery, patients received 36 Gy CSRT with boosts to sites of disease and, concomitantly, 15–30 doses of carboplatin (30–45 mg/m²/dose), along with vincristine once per week for 6 weeks. Patients on regimen A received 6 months of maintenance chemotherapy with cyclophosphamide and VCR. Once the recommended phase II dose of carboplatin was determined, cisplatin was added to the maintenance (regimen B). Five-year OS and PFS for 77 patients treated at the phase 2 found carboplatin dose on regimen A were 82% and 71% versus 68% and 59% on regimen B (P ns) (Jakacki et al., 2012 Jul 20). COG is also currently evaluating a randomised treatment of concurrent carboplatin + vincristine plus RT (vs. RT only) followed by maintenance CT with or without 13-cis retinoic acid (an anti-apoptotic agent) in children with newly diagnosed high-risk medulloblastoma and supratentorial PNETs (data unpublished).

None of these studies has so far provided more than a type 3 evidence concerning the contribution of high doses of craniospinal irradiation, possibly delivered through a hyperfractionated/accelerated modality, neither of high-dose CT schedules, to achieve better disease control. It is, therefore, desirable that wider phase 3 trials should be initiated to obtain stronger evidence. Any effort to improve prognosis through more intensive treatments should be accompanied by the most accurate quality assurance of the treatment given and its feasibility in order to avoid as much as possible undue toxicities. Until that time, our recommendations are to enrol these patients in controlled clinical trials, because of the dismal prognosis and the more aggressive treatment required, with accompanying acute and long-term side effects.

6.2.3. Treatment for younger children

Infants have either SHH tumours, which typically have nodular/desmoplastic or MBEN histology, tumour location in the cerebellar hemisphere, and a better prognosis, or group 3 tumours, which are frequently of LC/A histology, harbour MYC amplification, have higher incidence of metastatic disease, and a poor prognosis (Taylor et al., 2012; Gilbertson, 2004). In a recent large-scale genomic study of SHH medulloblastoma, PTCH1 mutation occurred at a roughly equal frequency in infants (36%), children (42%), and adults (54%) while SUFU mutations were found almost exclusively in infants (Archer et al., 2012).

In the past, the survival of infants with medulloblastoma was inferior compared to older children. Possible reasons that may explain this observation were: delay in diagnosis, increased surgical risk, increased toxicity due to RT, under-treatment, and a potentially “more aggressive” biology. A cut-off age level of 3 years had been introduced in the mid- 1980s because strategies to delay or omit irradiation had high priority in order to reduce unacceptable sequelae (Duffner et al., 1993; Grill et al., 2005; von Bueren et al., 2011).

Thus trials were performed in the USA in the 1980s, and after 1985 also in Europe, using up-front CT in order to delay or to avoid RT. The MOPP protocol, which was a pioneering project, was used on 12 cases, 8 of whom became long-term survivors (Ater et al., 1997). The first Paediatric Oncology Group (POG) baby protocol (POG1), which was the first large cooperative study that attempted to delay irradiation by using conventional CT, was followed by several American (Children’s Cancer Study Group – CCSG) and European cooperative studies (baby protocols of the Société Française d’Oncologie Pédiatrique – SFOP, of the Italian Association for Paediatric Oncology – AIEOP, and of the German Society of Paediatric Oncology and Haematology – GPOH; HIT-SKK ‘87 study) (Duffner et al., 1993; Chi et al., 2004; Duffner et al., 1999; Rutkowski et al., 2009; Garrè et al., 2006). The POG1 study required children <2 years of age to be treated with CT for 2 years, while children who were two to three years of age were treated for 1 year. Both groups were eligible for RT at the end of CT. Sixty-two cases were recruited. EFS and OS at 5 years were 30% and 69%, respectively. Radical resection was a favourable prognostic factor, as 69% of M0/T0 cases became long-term survivors (13 cases) (Duffner et al., 1999).

The CCSG study tested the “8 in 1” protocol. After a median follow-up of 6 years, a 3-year EFS of 22% was obtained and long term survival was below 30% in M0/T0 cases (Geyer et al., 2005). Standard CT in France (Baby SFOP Protocol) included alternating courses of carboplatin/procarbazine, etoposide/cisplatin, vincristine/cyclophosphamide for 18 months. Thirty-three out of 47 M0/T0 patients progressed during/after CT, but OS was 76%. The results in metastatic cases were unsatisfactory (PFS 16%), while localised failures in M0/T0 were successfully rescued by high dose CT, with or without re-operation, followed by focal irradiation. Neuro-psychological outcome was also reported (Grill et al., 2005). These initial studies showed that only a minority of patients with

M0/T0 could be cured with conventional CT, and that the disease could not be controlled in patients with residual tumour after surgery and/or metastases. Therefore, European and American studies intensified systemic CT (POG2), while others added intraventricular CT (Germany) or high-dose systemic methotrexate (Italy – AIEOPSN9501) (Garrè et al., 2006). A German study investigated intraventricular CT in 43 patients. Although this study showed no favourable impact on metastatic disease, it achieved the best known OS and EFS in M0/T0 patients without irradiation (14/17 were cured) (Rutkowski et al., 2005). Neuropsychological outcome was better than for cases treated with CSI (Rutkowski et al., 2009), and about the same as cases treated with systemic CT alone, or controls. Due to the limited number of cases and special aspects of using intraventricular CT, it remains to be clarified whether these data can be reproduced in a larger international co-operative study, while the results from SKK92 have been confirmed in HIT 2000 (von Bueren et al., 2011). The introduction of sequential HDCT for relapsed patients or “up-front” for patients with metastases is currently being investigated in the 2nd generation studies, and high response rates have been reported (Garrè et al., 2006; Dallorso et al., 2005; Kalifa et al., 1999; Garrè et al., 2009; Ridola et al., 2007). The French group has also demonstrated that reduced volumes of irradiation after HDCT contributed to long-term survival (Ridola et al., 2007). Current and future studies should clarify whether these regimens can also increase the proportion of patients that may be cured without RT in the M0/T0 group, as well as in the high-risk group. The Italian AIEOP infant pilot study, which used HDCT alone for M0/T0 patients that, in case of residual tumour, was followed by conformal RT on the residue and in case of metastases by CSI, showed that 5 year EFS had increased (70%) with respect to previous series where standard-dose schedules were adopted (Strother et al., 2001; Ridola et al., 2007). It has become to be highlighted the subset of infants that were cured in each study with peculiar histological and biological features that favoured survival. The HIT-SKK ‘92 study analysed the impact of the histological variants and reported a high frequency of desmoplastic medulloblastoma (40%). In addition, the prognosis for desmoplastic medulloblastoma was significantly better compared with classic medulloblastoma (Rutkowski et al., 2005). A recent single institution retrospective study reports a similar observation, confirming the high frequency of desmoplastic variants and particularly of MBEN in young ages and the high frequency of association between Gorlin Syndrome and MBEN, which was observed in 40% of cases (Garrè et al., 2009). A meta-analysis of all infant studies conducted in the United States, Germany, France, Italy, and United Kingdom between 1987 and 2004 evaluated outcomes of 270 children less than 5 years of age treated on clinical protocols using different strategies (Rutkowski et al., 2010). The 8-year EFS and OS were significantly better for infants with nodular/desmoplastic medulloblastoma (55% and 76%, respectively) as compared to those with classic (27% and 42%, respectively) or anaplastic tumours (14% and 14%, respectively). Patients with localised disease who had a complete resection of tumour (M0R0) had a significantly better outcome compared to those with incomplete resection and/or metastatic disease (M+R1). In fact, a subgroup of children with nodular/desmoplastic medulloblastoma with M0R0 disease can be cured with CT alone (Rutkowski et al., 2005). It appears that this histologic subtype, mostly associated with the SHH activation, is an important prognostic factor in young children conferring a better outcome irrespective of the therapeutic approach used. Further prospective cooperative studies addressing these issues will be performed.

In conclusion, the treatment of infant MB has evolved (role of RT revisited and more intensive CT adopted) during the last 10–15 years, and survival rates have been improved by modern treatment strategies; recent observations seem to show that age per se is no

Table 3
Late sequelae follow-up.

LATE SEQUELAE FOLLOW-UP	TO DOes from 1st year after completion of treatment
Neurosensory defects: hearing and visual	Constant monitoring → Early deficit correction
Neurocognitive outcome	Early assessment of attention, executive functioning, processing speed, working memory, reading and learning functions → Intervention program with drug therapy, cognitive and behavioural strategies, educational programmes
Endocrine evaluation: GH, gonadotropin, ACTH, TSH, PRL	GH evaluation: Gonadotropin, estradiol, testosterone, testicular volume treatment one year after completion of oncological treatment yearly assessment → GnRH agonists th. for precocious puberty and replacement therapy for delay
Thyroid nodules	Clinical evaluation for suspicious ACTH deficit and whole pituitary axis evaluation → hydrocortisone replacement FT4, TSH assessment and neck physical examination every 6 months → thyroxine replacement
Osteopenia/osteoporosis	PRL evaluation → dopamine agonists
Overweight/obesity	Yearly examination; ultrasound examination to be repeated every other year if normal → Fine needle aspiration and subsequent treatment Bone evaluation with DEXA → Calcium + Vitamin D treatment Blood glucose, insulin, lipidic profile every 2 years → dietary counselling, exercise, weight loss

longer an adverse prognostic factor. This is due to the impact of reserving more intensive treatment for advanced stage disease and unfavourable histology along with the presence of favourable histological variants (in up to 50% of cases). An international phase III trial for young children with medulloblastoma, comparing survival rates and neurocognitive outcomes of different treatment strategies using standardised criteria, is upcoming within SIOP.

Due to the higher frequency (28%) of cancer predisposition syndromes (mainly Gorlin Syndrome) in young patients (Garrè et al., 2009; Amlashi et al., 2003) with medulloblastoma, future trials should include guidelines for the identification of such conditions, and for genetic counselling to families. The increased risk of secondary tumours and the frequency of naevoid basal-cell carcinomas in irradiated fields push to avoid RT in infants when associated with Gorlin Syndrome.

7. Late sequelae

Long-term sequelae of patients treated for medulloblastoma, including motor, sensory, endocrinological, cognitive, neuropsychological and behavioural deficits, can markedly affect their quality of life and their re-entry into school and society.

The prognostication of risk by combining information from molecular grouping, cytogenetic biomarkers, and clinical risk factors allows for therapy intensification in high-risk children to improve survival and de-escalation of treatment in those with low-risk disease so as to avoid the significant complications of therapy.

The issue of the quality of survival has to be put in every prospective trial as one of the goals of treatment amelioration. In a recent report (Kennedy et al., 2014), Kennedy compared quality of survival in “standard-risk” medulloblastoma after hyperfractionated craniospinal radiation therapy with the same survival after standard radiation therapy, combined with a CT regimen common to both treatment arms, that constituted the PNET4 randomised controlled trial (Gatta et al., 2009). Data on executive function, health status, behaviour, health-related quality of life, and medical, educational, employment, and social information, were provided by 62% of 244 eligible survivors at median interval from diagnosis of 5.8 years. The conclusion was that hyperfractionated radiation therapy was associated with better executive function and worse growth, but without accompanying change in health status, behaviour, or quality of life. A twin paper (Câmara-Costa et al., 2015) evaluated intelligence quotient in children and young adults in this same trial, concluding that HFRT was associated with a trend towards better verbal outcomes in children aged less than 8 years at diagnosis, but no significant differences on the other cognitive measures. Many

uncertainties still remain about radiobiological assumptions and the real patients outcome.

Late sequelae follow-up is summarized in Table 3.

7.1. Endocrine sequelae

The occurrence of neuro-endocrine deficiencies following craniospinal irradiation for medulloblastoma is well known. Surgically induced deficiencies manifest shortly after surgery but can worsen also along time while radiation-induced damage may manifest months to years after irradiation. For this reason long-term endocrine surveillance after craniospinal irradiation is mandatory (Heikens et al., 1998).

Radiation-induced damage is currently considered a consequence of a direct neuronal rather than vascular injury to the hypothalamus (Darzy and Shalet, 2009). Subsequently, due to the prolonged absence of rh-GH-stimulating action, pituitary function may be affected. The hypothalamus-pituitary axis has a different radiosensitivity, with the GH axis being the most radiosensitive followed by the gonadotrophin, ACTH, and thyroid-stimulating hormone (TSH) axes.

7.2. GH deficiency (GHD)

GHD is observed in 40–80% of survivors of medulloblastoma (Fossati et al., 2009; Bull et al., 2007). Incidence of GHD depends on: age at RT, total dose delivered (>45 Gy), fields of RT, duration, fractions, and time after irradiation. It worsens with time and frequently becomes irreversible. GHD may develop from 3 months to 5 years after the end of RT.

Growth screening of irradiated children includes (Rose, 2003): antropometric measurements (height, weight, BMI, lower segment and arm span, Tanner staging) every 6 months until growth complete and/or sexually mature then once a year (always refer to endocrine, or at least if height/weight 2 percentile channels, growth <4–5 cm per year and/or lack of pubertal growth spurt), nutritional evaluation (every 6 months), laboratory tests (IGF-1 even if its role is debated, IGF binding protein 3, bone age determination, insulin tolerance test and GH provocative tests – sleep, exercise, arginine, clonidine, and levodopa).

Once diagnosed, the standard treatment of GHD consists of substitutive therapy with 0.18–0.3 mg/kg somatropin or 0.3 mg/kg somatrem, both daily.

Substitutive therapy is widely considered safe in terms of tumour recurrence and it can be started 1 year after completion of the oncological treatment with no evidence of further tumour

growth (Heikens et al., 1998; Sklar et al., 2002; Growth Hormone Research Society–GHRS, 2000).

Three other causes of growth failure must be ruled out before starting GH replacement therapy: 1. slowing of growth during the acute phase of radiotherapy secondary to poor caloric intake; 2. poor spinal (but not limb) growth after radiation of the spine secondary to destruction of growth plates in the spine following spinal irradiation; 3. Premature closure of the epiphyses due to precocious puberty.

7.3. Gonadal alterations

Gonadal alterations in children treated for medulloblastoma include: precocious puberty, delayed puberty, and hypogonadism. Incidence depends on: age at treatment (patients treated at younger ages are less susceptible due to sufficient follicular stores (Rutter and Rose, 2007)), concomitant radiochemotherapy, and RT doses. Gonadal alterations can be demonstrated after 1 year since the end of RT. The neuro-endocrinological evaluation in children with possible gonadal alterations includes: yearly estradiol levels assessment and pelvic ultrasonography in females, and yearly testicular volume, testosterone and β -HCG levels in males. For males and females annual height/weight assessment, LH and FSH basal and after GnRH stimulation, bone age, GH levels and Tanner stage should be monitored (Nandagopal et al., 2008).

Precocious puberty is defined as the development of secondary sexual traits before the age of 8 years in females and 9 years in males, accompanied by rapid growth in height. This alteration often coexists with GHD (in this case, if GHD is not treated, the child will not benefit of the pubertal growth spurt reaching a short final height). Early detection of precocious puberty is mandatory in order to avoid a short final stature. The treatment of central precocious puberty consists of the administration of long-acting analogs of GnRH agonists, such as leuprolide acetate (1.88–3.75 mg/i.m. monthly) as a standard treatment option.

Delayed puberty must be considered when the patient does not show secondary sexual development by age of 14 years for boys and 13 years for girls. Replacement therapy might prove useful, and standard treatment options include: conjugated estrogen (0.3 mg) or ethinyl estradiol (5–10 μ g) orally daily for females, and testosterone enanthate (100 mg) once in every 4 weeks for males.

Other detectable alterations in survivors of paediatric medulloblastoma are: infertility and precocious menopause. Sterility is more frequent in males and it is related to alkylating agents. Before treating sexually mature boys/girls with CT or irradiation, physicians should address the possibility of infertility with patients, including fertility-preservation options and appropriate referral to reproductive specialists (Rutter and Rose, 2007).

Hypothyroidism, such as altered thyroid function, during both craniospinal and cranial RT with central hypothyroidism after RT has been reported with a prevalence of about 6% (Anderson, 2003). The role of CT in inducing thyroid damage is debated. Incidence of hypothyroidism also depends on RT fractions delivered. In some studies, most thyroid dysfunctions have been detected within 4 years after RT. Recommendations for annual screening include a focused history for symptoms of hypothyroidism, physical examination (height, weight, skin, hair, and thyroid) and annual bone densitometry. FT4-TSH assessment should be performed every 6 months (Rutter and Rose, 2007; Nandagopal et al., 2008). The values should be maintained in the upper half of the normal range. Thyroid hormone recommended replacement is made with oral L-thyroxine once daily orally (0.05–0.1 mg), and in case of complete thyroid failure, 4–5 μ g/kg/day for children and 2–3 μ g/kg/day for adults (Anderson, 2003).

Hyperthyroidism may rarely occur after irradiation for paediatric medulloblastoma. Screening for hyperthyroidism consists of

yearly physical examination (eyes, skin, thyroid, heart, and neurologic examination) and FT3-FT4-TSH assessment (Nandagopal et al., 2008).

7.4. Thyroid nodules

Yearly thyroid physical examination should be performed. Periodical ultrasound examination is required, and fine needle aspiration should be considered in case of suspicious nodules (Nandagopal et al., 2008).

Hyperprolactinemia is a frequent finding after brain irradiation and may be due to the destruction of the hypothalamus-pituitary axis or to primary hypothyroidism. It has been described in both sexes and all age groups, but it is most frequently observed in the adult females (Rose, 2003). It has only been demonstrated more than 2 years after therapy. Screening includes periodic prolactin (PRL) and TSH assays, and when PRL levels are higher than 50 ng/ml, a pituitary MRI should be performed. Spontaneous resolution of the hyperprolactinemia at 5–6 years after RT is a sporadic finding, more often a standard treatment with a dopamine agonists is necessary (Bromocriptine 1.25–5 mg/day orally gradually increasing the dose, or Cabergoline 0.25–1 mg/week orally).

Central adrenal insufficiency (ACTH deficiency) is rare, but potentially life threatening. In one series it has been reported in 29% of medulloblastoma survivors (Rose et al., 2005).

Laboratory assessments include 8:00 a.m. cortisol levels. Given that central adrenal insufficiency has been detected in survivors many years after the completion of therapy, an 8:00 a.m. serum cortisol level should be obtained yearly until 15 years off therapy. If ACTH deficiency is suspected on clinical grounds, a test of the whole axis, such as the Insulin Tolerance Test or the metyrapone test, should be performed (Toogood, 2004).

Osteopenia/osteoporosis can be caused by both steroid therapy and craniospinal irradiation, while GH deficiency does not seem to be an important factor (Rose, 2003). Bone density evaluation by DEXA or quantitative CT should be performed during follow-up, starting at 2 years after completion of cancer therapy. The patient should be referred to a specialist if osteoporosis is suspected (T score \pm 2.5 DS or history of multiple fractures). Calcium and Vitamin D supplementation and optimisation of endocrine replacements are important as well (Nandagopal et al., 2008; Krishnamoorthy et al., 2004).

7.5. Overweight/obesity, dyslipidemia, and metabolic syndrome

Cranial RT but also the heavy metals carboplatin and cisplatin often used in medulloblastoma may cause dyslipidemia. Concurrent GH deficiency and hypothyroidism may exacerbate overweight/obesity (Lustig et al., 2003). The survivors' follow-up includes annual assessments of blood pressure and body mass index. Fasting blood glucose, serum insulin, and lipidic profile should be screened every 2 years in patients who are overweight or obese, and every 5 years in normal weight patients. Other comorbid conditions such as dyslipidemia, hypertension, glucose intolerance, diabetes mellitus, hyperinsulinism, and insulin resistance should be monitored. Counselling for dietary modification, exercise, and weight loss should be given while a pharmacologic intervention should be considered in patients unresponsive to dietary and lifestyle modifications (Nandagopal et al., 2008).

7.6. Neurocognitive outcome

Many survivors of medulloblastoma treatment experience long-term cognitive, neuropsychological, and academic impairments worsening over time. The ultimate neurocognitive outcome is very

complex and depends on a number of factors that interact in unpredictable ways.

The domains that are affected the most by treatment are: attention, executive functioning, processing speed, working memory, and learning, which adversely influence academic performance (Palmer et al., 2007; Palmer, 2008; Mabbott et al., 2008). Because of deficits in these important functional domains, survivors experience declines in Intelligence Quotient (IQ) and academic achievement relative to their same-age peers. This does not mean that the cognitive growth rate is arrested or declines as in dementia, but it is reduced compared with same-age peers. Therefore, as the time since treatment increases, the gap in abilities between the survivors and the general population increases, challenging problem solving, academic achievement, independent living, and the quality of life in general.

In some children the IQ drops by as much as 3–4 points per year: brain calcifications, leucoencephalopathy, and reductions in white matter volume correlate with these declines (Anderson, 2003).

The cause is bound to any of the treatment modalities; the main risk factors for their onset include:

1. (younger) age at diagnosis and treatment: the earlier the brain damage, the worse and more generalised is the cognitive impairment. The brain damage caused by the tumour site, the presence of clinical complications and oncological treatment arrests the physiological development of brain structures and functions, affecting or halting the processes leading to new skills acquisition, with a negative domino effect on cognitive development (Palmer, 2008; Mulhern et al., 2001);
2. tumour site: tumour invasion of normal brain/compression of the tumour on the brain parenchyma and trauma from surgical resection. The cerebellum plays an important role in higher cognitive functions given the reciprocal connections with the frontal lobe, and there can be long-term deficits in speech, language and communication, executive function, visuospatial ability, and behavioural regulation (Palmer, 2008; Reeves et al., 2006). A major complication is posterior fossa syndrome. This is characterised by mutism developing 48–72 h after resection, and it is associated with severe cerebellar deficits such as dysmetria, hypotonia, paresis, and mood depression, which can last several months. It is probably secondary to disruption of reticular substance pathways. Surgical technique does not seem to have a definite role; in particular, the use of a telovelar approach as compared to vermian split to reach the fourth ventricle extension of the tumour has not been demonstrated to prevent the development of cerebellar mutism. Concerning long-term prognosis, around one third of the children who develop cerebellar mutism after surgery have a persistent dysarthria, the remaining ones showing a residual phonological impairment. Long-term dysarthric features tend to be more severe and less prone to recovery in children presenting at diagnosis with associated combined procedural memory and defective neurocognitive functions (Tamburrini et al., 2015).
3. clinical complications: hydrocephalus. Posterior cranial fossa tumours can cause an obstruction of the 4th ventricle with ensuing hydrocephalus. This, in turn, may cause a generalised damage and nonspecific cognitive problems added to the structural and functional damage that is specifically related to the tumour site (Hardy et al., 2008);
4. cranial radiation therapy (CRT): the most prominent deficits for children with brain tumours are associated with cranial RT; patients receiving CRT are significantly more likely to have school problems than other brain tumour patients and experience a pervasive decline in knowledge acquisition. Poor intellectual outcome is associated with higher radiation doses and a larger volume as well as younger age at RT. The effects

of CRT begin to clinically impact cognitive functioning at about 1 year post-treatment and show a continuing pattern of decline over time. Younger patients experience an immediate decline that continued over time, while older patients experienced a delay in decline for about 2 years (Mulhern et al., 1998; Jain et al., 2008);

5. sensory and motor impairments: such deficits heavily impact on the later learning experience and the natural cognitive decline (Palmer et al., 2007).

In general, two processes could account for the cognitive decline experienced by patients with medulloblastoma. Children who show a decline in their standardised IQ scores could be losing previously acquired information as evidenced by a decline in raw scores. They could continue otherwise to acquire new information, but at a rate slower than expected when compared with normal same-age peers. School completion is highly dependent on the achievement of basic academic skills, including reading and spelling (Palmer et al., 2007). These skills have served as important endpoints in comprehensive studies of cognitive ability following treatment for medulloblastoma (Palmer et al., 2007; Jain et al., 2008). Patients younger than 7 years show a greater impairment in reading than patients with an older age at diagnosis. It has been speculated that, in children treated for medulloblastoma, the inability to acquire new information and skills at a rate comparable to healthy same-age peers may be due to deficits in underlying core abilities such as memory, attention and speed of processing.

Given these issues, targeted functional assessments should be carried out periodically in order to test for cognitive problems, if any, and start specific rehabilitation together with appropriate school support.

Besides interventions aimed at reducing the neurotoxicity to the CNS, effective intervention programmes may be considered the second line of defence against the cognitive decline following treatment. An early assessment of a child's deficits and strengths is necessary to help parents and teachers provide proper care, support and recovery from hospitalisation. Generally, children who survive paediatric medulloblastoma are impaired, so they necessitate long-term multidisciplinary follow-up and treatment for psychological and emotional difficulties. The degree of impairment varies, however, between patients. Patients at heightened risk of developing specific cognitive deficits should be accurately screened to start intervention programmes that can include drug therapy, cognitive therapy to enhance attention through metacognitive strategies, and cognitive-behavioural strategies, along with personalised educational and support programmes (Mulhern et al., 2005).

Furthermore, patients treated for medulloblastoma frequently show psychological and behavioural problems, such as inadequate social competence, withdrawal, anxiety, and depression that affect social adjustment and interpersonal skills. Given the complexity and variability of these deficits, a range of rehabilitative services should be offered, including speech and language therapy, occupational therapy, physical therapy, psychotherapy, and educational remediation.

7.7. Neurosensorial late effects

Auditory deficits are the most frequent late effects and are associated both with cochlear irradiation during boost to posterior fossa and cisplatin use (Packer et al., 2003b). Hypoacusia can be monolateral or bilateral and so severe as to require hearing aid. Audiometry is, therefore, constantly required during treatment and with regular follow-up examinations to provide early correction of deficits.

Visual defects relating to acuity are mainly due to intracranial hypertension, while nystagmus and diplopia may be found secondary to mass effects and tumour removal. Other defects, such

as dysmetria and ataxia, are frequently ameliorated by early re-education.

7.8. Orthopaedic late-effects

Craniospinal irradiation can be a concomitant cause of kyphosis and of vertebral demineralisation. This may also be caused by steroidal therapy, GH, and gonadotropin deficits, or altered food intake. Vertebral growth is obviously altered by irradiation and not helped by growth hormone replacement (Odame et al., 2006).

7.9. Second tumours

The use of both irradiation and CT (alkylating agents, nitrosureas, etoposide) contributes to the occurrence of secondary tumours (Goldstein et al., 1997). Meningiomas, cavernomas, and glial tumours are found in radiation fields as long as thirty years after treatment, and justify the prolongation of follow-up.

Secondary tumours due to treatment have to be distinguished from those arising in cancer predisposition syndromes like Gorlin and Turcot syndromes.

8. Follow-up

Relapses of medulloblastoma occur and more than half of these relapses have a component of disseminated disease. Relapses occur in nearly 75% of paediatric cases within 2 years. Relapse is most commonly diagnosed by neuroimaging; occasionally, clinical progression precedes neuroimaging findings. There are no formal clinical trials that address the specific question of the frequency of MRI use for radiographic surveillance (Minn et al., 2001).

Patients enrolled in study protocols have a formal timetable for imaging, although the intervals between MRI scans become arbitrary when a patient has completed the therapy. We generally recommend imaging of the brain and spine every 3 months for the first 2 years. Later, MRI of the brain should be performed every 4 months for the third year, every 6 months until the fifth year and then annually. Evaluation of the spine is generally required only in case of clinical suspicion.

Part of follow-up is all the clinical, radiological, and biochemical examinations, together with tailored tests for neuro-functional capabilities as detailed in the «late effects» section.

8.1. Treatment at relapse

The approach to treatment of a patient with relapsing medulloblastoma varies and depends on a range of factors. First, the age of the patient is important when deciding to use radiation therapy, which can cause severe neurological morbidity in children younger than 3 years old and is therefore avoided at diagnosis in this age category standard-risk patients, but can be used at relapse as retrieval, combined with various CT schedules mostly with myeloablative dosages (Ridola et al., 2007). This option, which has been used with some success, is to be considered investigational only and it is not successful in older children that have already received craniospinal irradiation. In this age group, in fact, approximately 20% of patients who experience relapse after irradiation cannot be cured by salvage therapy, barring very rare exceptions (<5% of those who experience relapse) (Minn et al., 2001; Bouffet et al., 1998; Massimino et al., 2009; Pizer et al., 2011).

In older children who received craniospinal radiation as part of their initial therapy, re-operation, followed by focal radiation with conformal techniques or proton beam, might be an option for solitary recurrences and should be considered on a case-by-case basis (Saran et al., 2008). However, in these circumstances, the CSF must be examined before starting therapy to assess the extent of dissemination.

Trials of idarubicin, taxol, topotecan, temozolomide, and irinotecan recorded few responses with nearly all patients developing further tumour progression (Kadota et al., 1999; Hurwitz et al., 2001; Dreyer et al., 2003; Nicholson et al., 2007; Bomgaars et al., 2007; Massimino et al., 2013b; Cefalo et al., 2014). Another approach under investigation is the use of a low-dose CT regimen called “metronomic” therapy. Several groups have reported the feasibility of this approach for treating paediatric brain tumours in case series (Kieran et al., 2005) and a formalised clinical trial is ongoing in Europe (Peyrl et al., 2012). The main concerns about this approach are the immediate haematological toxicities and the long-term risk of secondary malignancies. The open clinical trial will probably validate this option.

Although “druggable” mutations and copy number variations are present in the genomic landscape of this disease, the only targeted therapy that has been evaluated in the clinic includes the Smoothened (SMO) inhibitors. In a phase I (33 children, SHH medulloblastoma in 7) followed by a phase II trial (12: all SHH medulloblastoma) of GDC0449 (PBTC-025 and -032), only one patient had a defined protocol sustained objective response, as compared to 3 of 20 adults with recurrent SHH medulloblastoma (PBTC-025B, phase II) whose tumours exhibited objective response to this agent. In a phase I trial of LDE225, Shou et al. reported that 6/50 patients with recurrent medulloblastoma who had a five-gene signature identifying the SHH pathway experienced a sustained response to the agent (Gajjar et al., 2013; Shou et al., 2015). It is now apparent that SMO inhibitors work only in the context of PTCH or SMO mutations (more common in adult medulloblastoma) and not at all if SHH pathway activation is due to mutations in downstream targets, including SUFU, GLI2, or MYCN (as seen in childhood tumours). Responses to SMO inhibitors, even when they occur, are transient due to development of acquired resistance (Yauch et al., 2009; Metcalfe et al., 2013). It is, therefore, unlikely that single agent therapy will provide sustained benefit. Patient management at relapse, therefore, typically focuses on quality of remaining life rather than curative strategies. This absence of suitable treatment alternatives has stemmed primarily from the scarcity of biological data, because biopsy is rarely performed at this stage. Consequently, this has impeded the characterization of mechanisms that drive medulloblastoma relapse until recently. A very recent study has shown, however, through the study of 29 recurrent tumours and their primaries, that combined MYC and P53 defects commonly emerge at medulloblastoma relapse defining a patient group with clinically aggressive tumours but potentially treatable with target therapies (Hill et al., 2015). In conclusion the authors claim that the routine sampling of relapsed medulloblastoma could be considered as essential to inform comprehensive biological investigations across all clinical and molecular disease demographics, and to drive therapeutic advances aimed at improved outcomes for children with relapsed medulloblastoma. An even more paper has also shown that whole-genome sequencing of 33 pairs of human diagnostic and post-therapy medulloblastomas demonstrated substantial genetic divergence of the dominant clone after. In both mice and humans, the dominant clone at recurrence arose through clonal selection of a pre-existing minor clone present at diagnosis. Targeted therapy is therefore unlikely to be effective in the absence of the target, being the relapse tumour clonally different from the primary and the authors conclude that for all future clinical trials of targeted therapy of recurrent medulloblastoma, it should be mandatory to include re-biopsy to demonstrate maintenance of the target in the dominant recurrent clone (Morrissey et al., 2016).

However, the paucity and modest efficacy of currently available novel targeted agents for recurrent medulloblastoma is a sobering fact and has to be balanced against the risk of long-term toxicity due to these agents, especially in young children.

Acknowledgement

This research was supported by the European Commission with the project “Information network on rare cancers”, grant number 2000111201.

References

- Albright, A.L., Sposto, R., Holmes, E., Zeltzer, P.M., Finlay, J.L., Wisoff, J.H., et al., 2000. Correlation of neurosurgical subspecialization with outcomes in children with malignant brain tumors. *Neurosurgery* 47 (4), 885–887.
- Amlashi, S.F., Riffaud, L., Brassier, G., Morandi, X., 2003. Nevoid basal cell carcinoma syndrome: relation with desmoplastic medulloblastoma in infancy: a population-based study and review of the literature. *Cancer* 98 (3), 618–624.
- Anderson, N.E., 2003. Late complications in childhood central nervous system tumour survivors. *Curr. Opin. Neurol.* 16 (6), 677–683.
- Archer, T.C., Weeraratne, S.D., Pomeroy, S.L., 2012. Hedgehog-Gli pathway in medulloblastoma. *J. Clin. Oncol.* 30 (17), 2154–2156.
- Ater, J.L., van Eys, J., Woo, S.Y., Moore 3rd, B., Copeland, D.R., Bruner, J., 1997. MOPP chemotherapy without irradiation as primary postsurgical therapy for brain tumors in infants and young children. *J. Neurooncol.* 32 (3), 243–252.
- Baldwin, R.T., Preston-Martin, S., 2004. Epidemiology of brain tumors in childhood –a review. *Toxicol. Appl. Pharmacol.* 199 (2), 118–131.
- Bomgaars, L.R., Bernstein, M., Krailo, M., Kadota, R., Das, S., Chen, Z., et al., 2007. Phase II trial of irinotecan in children with refractory solid tumors: a children's oncology group study. *J. Clin. Oncol.* 25 (29), 4622–4627.
- Bouffet, E., Doz, F., Demaille, M.C., Tron, P., Roche, H., Plantaz, D., et al., 1998. Improving survival in recurrent medulloblastoma: earlier detection, better treatment or still an impasse? *Br. J. Cancer* 77 (8), 1321–1326.
- Buhring, U., Strayle-Batra, M., Freudenstein, D., Scheel-Walter, H.G., Küker, W., 2002. MRI features of primary: secondary and metastatic medulloblastoma. *Eur. Radiol.* 12 (6), 1342–1348.
- Bull, K.S., Spoudeas, H.A., Yadegarfar, G., Kennedy, C.R., 2007. CCLG. Reduction of health status 7 years after addition of chemotherapy to craniospinal irradiation for medulloblastoma: a follow-up study in PNET 3 trial survivors on behalf of the CCLG (formerly UKCCSG). *J. Clin. Oncol.* 25 (27), 4239–4245.
- Câmara-Costa, H., Resch, A., Kieffer, V., Lalande, C., Poggi, G., Kennedy, C., Bull, K., Calaminus, G., Grill, J., Doz, F., Rutkowski, S., Massimino, M., Kortmann, R.D., Lannering, B., Dellatolas, G., Cheignard, M., 2015. Quality of survival working group of the brain tumour group of SIOP-Europe: neuropsychological outcome of children treated for standard risk medulloblastoma in the PNET4 european randomized controlled trial of hyperfractionated versus standard radiation therapy and maintenance chemotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 92 (5), 978–985.
- Carrie, C., Muracciole, X., Gomez, F., Habrand, J.L., Benhassel, M., Mege, M., Mahé, M., Quetin, P., Maire, J.P., Soum, F., Baron, M.H., Clavere, P., Chapet, S., Gaci, Z., Kolodie, H., Maingon, P., Vie, B., Bernier, V., Alapetite, C., Hoffstetter, S., Grill, J., Lafay, F., French Society of Pediatric Oncology, 2005. Conformal radiotherapy, reduced boost volume, hyperfractionated radiotherapy, and online quality control in standard-risk medulloblastoma without chemotherapy: results of the French M-SFOP 98 protocol. *Int. J. Radiat. Oncol. Biol. Phys.* 63 (November (3)), 711–716, Epub 2005 May 31.
- Cefalo, G., Massimino, M., Ruggiero, A., Barone, G., Ridola, V., Spreafico, F., et al., 2014. Temozolomide is an active agent in children with recurrent medulloblastoma/primitive neuroectodermal tumor: an Italian multi-institutional phase II trial. *Neuro Oncol.* 16 (5), 748–753.
- Chang, C.H., Housepian, E.M., Herbert Jr., C., 1969. An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. *Radiology* 93 (6), 1351–1359.
- Chi, S.N., Gardner, S.L., Levy, A.S., Knopp, E.A., Miller, D.C., Wisoff, J.H., 2004. et al., Feasibility and response to induction chemotherapy intensified with high-dose methotrexate for young children with newly diagnosed high-risk disseminated medulloblastoma. *J. Clin. Oncol.* 22 (24), 4881–4887, Erratum in: *J Clin Oncol* 2005; 23(12): 2877.
- Clifford, S.C., Lannering, B., Schwalbe, E.C., Hicks, D., Toole, K.O., Nicholson, S.L., Goshchik, T., Zur Mühlen, A., Figarella-Branger, D., Doz, F., Rutkowski, S., Gustafsson, G., Pietsch, T., 2015. Biomarker-driven stratification of disease-risk in non-metastatic medulloblastoma: results from the multi-center HIT-SIOP-PNET4 clinical trial. *Oncotarget* 6 (36), 38827–38839.
- Cordier, S., Lefeuve, B., Filippini, G., Peris-Bonet, R., Farinotti, M., Lovicu, G., et al., 1997. Parental occupation, occupational exposure to solvents and polycyclic aromatic hydrocarbons and risk of childhood brain tumors (Italy, France, Spain). *Cancer Causes Control* 8 (5), 688–697, Erratum in: *Cancer Causes Control* 1997; 8(6): 934.
- Dallorso, S., Dini, G., Ladenstein, R., Cama, A., Milanaccio, C., Barra, S., et al., 2005. Evolving role of myeloablative chemotherapy in the treatment of childhood brain tumours. *Bone Marrow Transplant.* 35 (Suppl. (1)), S31–S34.
- Darzy, K.H., Shalet, S.M., 2009. Hypopituitarism following radiotherapy revisited. *Endocr. Dev.* 15, 1–24.
- Dhodapkar, K., Dunkel, I.J., Gardner, S., Sapp, M., Thoron, L., Finlay, J., 2002. Preliminary results of dose intensive pre-irradiation chemotherapy in patients older than 10 years of age with high risk medulloblastoma and supratentorial primitive neuroectodermal tumors. *Med. Pediatr. Oncol.* 38 (1), 47–48.
- Dietrich, M., Block, G., Pogoda, J.M., Buffler, P., Hecht, S., Preston-Martin, S., 2005. A review: dietary and endogenously formed N-nitroso compounds and risk of childhood brain tumors. *Cancer Causes Control* 16 (6), 619–635.
- Dreyer, Z.E., Kadota, R.P., Stewart, C.F., Friedman, H.S., Mahoney, D.H., Kun, L.E., et al., 2003. Phase 2 study of idarubicin in pediatric brain tumors: pediatric oncology group study POG 9237. *Neuro Oncol.* 5 (4), 261–267.
- Duffner, P.K., Horowitz, M.E., Krischer, J.P., Friedman, H.S., Burger, P.C., Cohen, M.E., et al., 1993. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. *N. Engl. J. Med.* 328 (24), 1725–1731.
- Duffner, P.K., Horowitz, M.E., Krischer, J.P., Burger, P.C., Cohen, M.E., Sanford, R.A., et al., 1999. The treatment of malignant brain tumors in infants and very young children: an update of the Pediatric Oncology Group experience. *Neuro Oncol.* 1 (2), 152–161.
- Dufour, C., Kieffer, V., Varlet, P., Raquin, M.A., Dhermain, F., Puget, S., et al., 2014. Tandem high-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk medulloblastoma or supratentorial primitive neuro-ectodermal tumors. *Pediatr. Blood Cancer* 61 (8), 1398–1402.
- Eberhart, C.G., Kepner, J.L., Goldthwaite, P.T., Kun, L.E., Duffner, P.K., Friedman, H.S., et al., 2002a. Histopathologic grading of medulloblastomas: a Pediatric Oncology Group study. *Cancer* 94 (2), 552–560.
- Eberhart, C., Kratz, J., Schuster, A., et al., 2002b. Comparative genomic hybridization detects an increased number of chromosomal alterations in large cell/anaplastic medulloblastomas. *Brain Pathol.* 12, 36–44.
- Ellison, D.W., Dalton, J., Kocak, M., Nicholson, S.L., Fraga, C., Neale, G., et al., 2011. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. *Acta Neuropathol.* 121 (3), 381–396.
- Evans, A.E., Jenkin, R.D., Sposto, R., Ortega, J.A., Wilson, C.B., Wara, W., et al., 1990. The treatment of medulloblastoma. Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. *J. Neurosurg.* 72 (4), 572–582.
- Ezzat, S., Kamal, M., El-Khateeb, N., El-Beltagy, M., Taha, H., Refaat, A., Awad, M., Abouelnaga, S., Zaghloul, M.S., 2016. Pediatric brain tumors in a low/middle income country: does it differ from that in developed world? *J. Neurooncol.* 126 (2), 371–376.
- Fear, N.T., Roman, E., Ansell, P., Bull, D., 2001. Malignant neoplasms of the brain during childhood: the role of prenatal and neonatal factors (United Kingdom). *Cancer Causes Control* 12 (5), 443–449.
- Fossati, P., Ricardi, U., Orecchia, R., 2009. Pediatric medulloblastoma: toxicity of current treatment and potential role of protontherapy. *Cancer Treat Rev.* 35 (1), 79–96.
- Gajjar, A.J., Robinson, G.W., 2014. Medulloblastoma-translating discoveries from the bench to the bedside. *Nat. Rev. Clin. Oncol.* 11 (12), 714–722.
- Gajjar, A., Fouladi, M., Walter, A.W., Thompson, S.J., Reardon, D.A., Merchant, T.E., et al., 1999. Comparison of lumbar and shunt cerebrospinal fluid specimens for cytologic detection of leptomeningeal disease in pediatric patients with brain tumors. *J. Clin. Oncol.* 17 (6), 1825–1828.
- Gajjar, A., Chintagumpala, M., Ashley, D., Kellie, S., Kun, L.E., Merchant, T.E., et al., 2006. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol.* 7 (10), 813–820, Erratum in: *Lancet Oncol* 2006; 7(10): 797.
- Gajjar, A., Stewart, C.F., Ellison, D.W., Kaste, S., Kun, L.E., Packer, R.J., et al., 2013. Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a pediatric brain tumor consortium study. *Clin. Cancer Res.* 19 (22), 6305–6312.
- Gandola, L., Massimino, M., Cefalo, G., Solero, C., Spreafico, F., Pecori, E., et al., 2009. Hyperfractionated accelerated radiotherapy in the Milan strategy for metastatic medulloblastoma. *J. Clin. Oncol.* 27 (4), 566–571.
- Garré, M.L., Cama, A., Milanaccio, C., Gandola, L., Massimino, M., Dallorso, S., 2006. New concepts in the treatment of brain tumors in very young children. *Expert Rev. Neurother.* 6 (4), 489–500.
- Garré, M.L., Cama, A., Bagnasco, F., Morana, G., Giangaspero, F., Brisigotti, M., et al., 2009. Medulloblastoma variants: age-dependent occurrence and relation to Gorlin syndrome—a new clinical perspective. *Clin. Cancer Res.* 15 (7), 2463–2471.
- Gatta, G., Zigon, G., Capocaccia, R., Coebergh, J.W., Desandes, E., Kaatsch, P., et al., 2009. Survival of European children and young adults with cancer diagnosed 1995–2002. *Eur. J. Cancer* 45 (6), 992–1005.
- Gatta, G., Botta, L., Rossi, S., Aareleid, T., Bielska-Lasota, M., Clavel, J., et al., 2014. Childhood cancer survival in Europe 1999–2007: results of EUROcare-5? a population-based study. *Lancet Oncol.* 15 (1), 35–47.
- Gentet, J.C., Bouffet, E., Doz, F., Tron, P., Roche, H., Thyss, A., et al., 1995. Preirradiation chemotherapy including eight drugs in 1 day regimen and high-dose methotrexate in childhood medulloblastoma: results of the M7 French Cooperative Study. *J. Neurosurg.* 82 (4), 608–614.
- Gessi, M., Giangaspero, F., Pietsch, T., 2003. Atypical teratoid/rhabdoid tumors and choroid plexus tumors: when genetics surprise pathology. *Brain Pathol.* 13, 409–414.
- Geyer, J.R., Sposto, R., Jennings, M., Boyett, J.M., Axtell, R.A., Breiger, D., et al., 2005. Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the children's cancer group. *J. Clin. Oncol.* 23 (30), 7621–7631.

- Giangaspero, F., Eberhart, C.G., Ellison, D.W., Haapasalo, H., Pietsch, T., 2007. Wiestler OD. In: Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavane, W.K. (Eds.), *WHO Classification of Tumours of the Nervous System*. IARC, Lyon.
- Gibson, P., Tong, Y., Robinson, G., Thompson, M.C., Currie, D.S., Eden, C., et al., 2010. Subtypes of medulloblastoma have distinct developmental origins. *Nature* 468 (7327), 1095–1099.
- Gilbertson, R.J., Ellison, D.W., 2008. The origins of medulloblastoma subtypes. *Annu. Rev. Pathol.* 3, 341–365.
- Gilbertson, R.J., 2004. Medulloblastoma: signalling a change in treatment. *Lancet Oncol.* 5 (4), 209–218.
- Giordano, M.T., Schiffer, P., Lanotte, M., Girardi, P., Chio, A., 1999. Epidemiology of adult medulloblastoma. *Int. J. Cancer* 80, 689–692.
- Goldstein, A.M., Yuen, J., Tucker, M.A., 1997. Second cancers after medulloblastoma: population-based results from the United States and Sweden. *Cancer Causes Control* 8 (6), 865–871.
- Grill, J., Sainte-Rose, C., Jouvett, J.C., Lejars, O., Frappaz, D., et al., 2005. Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children. *Lancet Oncol.* 6 (8), 573–580.
- Growth Hormone Research Society—GHRS, 2000. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J. Clin. Endocrinol. Metab.* 85 (11), 3990–3993.
- Harder, T., Plagemann, A., Harder, A., 2008. Birth weight and subsequent risk of childhood primary brain tumors: a meta-analysis. *Am. J. Epidemiol.* 168 (4), 366–373.
- Harding, N.J., Birch, J.M., Hepworth, S.J., McKinney, P.A., 2009. Infectious exposure in the first year of life and risk of central nervous system tumors in children: analysis of day care, social contact, and overcrowding. *Cancer Causes Control* 20 (2), 129–136.
- Hardy, K.K., Bonner, M.J., Willard, V.W., Watral, M.A., Gururangan, S., 2008. Hydrocephalus as a possible additional contributor to cognitive outcome in survivors of pediatric medulloblastoma. *Psychooncology* 17 (11), 1157–1161.
- Heikens, J., Michiels, E.M., Behrendt, H., Endert, E., Bakker, P.J., Fliers, E., 1998. Long-term neuro-endocrine sequelae after treatment for childhood medulloblastoma. *Eur. J. Cancer* 34 (10), 1592–1597.
- Hill, R.M., Kuijper, S., Lindsey, J.C., Petrie, K., Schwalbe, E.C., Barker, K., Boulton, J.K., Williamson, D., Ahmad, Z., Hallsworth, A., Ryan, S.L., Poon, E., Robinson, S.P., Ruddle, R., Raynaud, F.I., Howell, L., Kwok, C., Joshi, A., Nicholson, S.L., Crosier, S., Ellison, D.W., Wharton, S.B., Robson, K., Michalski, A., Hargrave, D., Jacques, T.S., Pizer, B., Bailey, S., Swartling, F.J., Weiss, W.A., Chesler, L., Clifford, S.C., 2015. Combined MYC and P53 defects emerge at medulloblastoma relapse and define rapidly progressive, therapeutically targetable disease. *Cancer Cell* 27 (1), 72–84.
- Hurwitz, C.A., Strauss, L.C., Kepner, J., Kretschmar, C., Harris, M.B., Friedman, H., et al., 2001. Paclitaxel for the treatment of progressive or recurrent childhood brain tumors: a pediatric oncology phase II study. *J. Pediatr. Hematol. Oncol.* 23 (5), 277–281.
- Jain, N., Krull, K.R., Brouwers, P., Chintagumpala, M.M., Woo, S.Y., 2008. Neuropsychological outcome intensity-modulated radiation therapy for pediatric medulloblastoma. *Pediatr. Blood Cancer* 51 (2), 275–279.
- Jakacki, R.I., Burger, P.C., Zhou, T., Holmes, E.J., Kocak, M., Onar, A., Goldwein, J., Mehta, M., Packer, R.J., Tarbell, N., Fitz, C., Vezina, G., Hilden, J., Pollack, I.F., 2012 Jul 20. Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study. *J. Clin. Oncol.* 30 (21), 2648–2653.
- Jones, D.T., Jäger, N., Kool, M., Zichner, T., Hutter, B., Sultan, M., et al., 2012. Dissecting the genomic complexity underlying medulloblastoma. *Nature* 488 (7409), 100–105.
- Judkins, A.R., Mauger, J., Ht, A., Rorke, L.B., Biegel, J.A., 2004. Immunohistochemical analysis of hSNF5/INI1 in pediatric CNS neoplasms. *Am. J. Surg. Pathol.* 28, 644–650.
- Kadota, R.P., Stewart, C.F., Horn, M., Kuttlesch Jr., J.F., Burger, P.C., Kepner, J.L., et al., 1999. Topotecan for the treatment of recurrent or progressive central nervous system tumors—a pediatric oncology group phase II study. *J. Neurooncol.* 43 (1), 43–47.
- Kalifa, C., Valteau, D., Pizer, B., Vassal, G., Grill, J., Hartmann, O., 1999. High-dose chemotherapy in childhood brain tumors. *Childs Nerv. Syst.* 15 (10), 498–505.
- Kennedy, C., Bull, K., Cheignard, M., Culliford, D., Dörr, H.G., Doz, F., et al., 2014. PNET4 study group of the Brain Tumour Group of The European branch of the International Society of Paediatric Oncology (SIOP-E). Quality of survival and growth in children and young adults in the PNET4 European controlled trial of hyperfractionated versus conventional radiation therapy for standard-risk medulloblastoma. *Int. J. Radiat. Oncol. Biol. Phys.* 88 (2), 292–300.
- Kieran, M.W., Turner, C.D., Rubin, J.B., Chi, S.N., Zimmerman, M.A., Chordas, C., et al., 2005. A feasibility trial of antiangiogenic (metronomic) chemotherapy in pediatric patients with recurrent or progressive cancer. *J. Pediatr. Hematol. Oncol.* 27 (11), 573–581.
- Koeller, K.K.I., Rushing, E.J., 2003. From the archives of the AFIP: medulloblastoma: a comprehensive review with radiologic-pathologic correlation. *Radiographics* 23 (November–December (6)), 1613–1637.
- Kohler, B.A., Ward, E., McCarthy, B.J., et al., 2011. Annual report to the nation on the status of cancer, 1975–2007 featuring tumors of the brain and other nervous system. *J. Natl. Cancer Inst.* 103 (9), 714–736.
- Kool, M., Korshunov, A., Remke, M., Jones, D.T., Schlanstein, M., Northcott, P.A., et al., 2012. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. *Acta Neuropathol.* 123 (4), 473–484.
- Kool, M., Jones, D.T., Jäger, N., Northcott, P.A., Pugh, T.J., Hovestadt, V., et al., 2014. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. *Cancer Cell* 25 (3), 393–405.
- Korshunov, A., Remke, M., Werft, W., Benner, A., Ryzhova, M., Witt, H., Sturm, D., Wittmann, A., Schottler, A., Felsberg, J., Reifenberger, G., Rutkowski, S., Scheurlen, W., Kulozik, A.E., von Deimling, A., Lichter, P., et al., 2010. Adult and pediatric medulloblastomas are genetically distinct and require different algorithms for molecular risk stratification. *J. Clin. Oncol.* 28, 3054–3060.
- Kortmann, R.D., Kuhl, J., Timmermann, B., Mittler, U., Urban, C., Budach, V., et al., 2000. Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91. *Int. J. Radiat. Oncol. Biol. Phys.* 46 (2), 269–279.
- Krishnamoorthy, P., Freeman, C., Bernstein, M.L., Lawrence, S., Rodd, C., 2004. Osteopenia in children who have undergone posterior fossa or craniospinal irradiation for brain tumors. *Arch. Pediatr. Adolesc. Med.* 158 (5), 491–496.
- Lannering, B., Rutkowski, S., Doz, F., Pizer, B., Gustafsson, G., Navajas, A., et al., 2012. Hyperfractionated versus conventional radiotherapy followed by CT in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. *J. Clin. Oncol.* 30 (26), 3187–3193.
- Leary, S.E., Zhou, T., Holmes, E., Geyer, J.R., Miller, D.C., 2011. Histology predicts a favorable outcome in young children with desmoplastic medulloblastoma: a report from the children's oncology group. *Cancer* 117, 3262–3267.
- Li, P., McLaughlin, J., Infante-Rivard, C., 2009. Maternal occupational exposure to extremely low frequency magnetic fields and the risk of brain cancer in the offspring. *Cancer Causes Control* 20 (6), 945–955.
- Lustig, R.H.I., Post, S.R., Srivannaboon, K., Rose, S.R., Danish, R.K., Burghen, G.A., Xiong, X., Wu, S., Merchant, T.E., 2003. Risk factors for the development of obesity in children surviving brain tumors. *J. Clin. Endocrinol. Metab.* 88 (2), 611–616.
- Mabbott, D.J., Penkman, L., Witol, A., Strother, D., Bouffett, E., 2008. Core neurocognitive functions in children treated for posterior fossa tumors. *Neuropsychology* 22 (2), 159–168.
- Massimino, M., Gandola, L., Spreafico, F., Biassoni, V., Luksch, R., Collini, P., et al., 2009. No salvage using high-dose chemotherapy plus/minus reirradiation for relapsing previously irradiated medulloblastoma. *Int. J. Radiat. Oncol. Biol. Phys.* 73 (5), 1358–1363.
- Massimino, M., Antonelli, M., Gandola, L., Miceli, R., Pollo, B., Biassoni, V., et al., 2013a. Histological variants of medulloblastoma are the most powerful clinical prognostic indicators. *Pediatr. Blood Cancer* 60 (2), 210–216.
- Massimino, M., Casanova, M., Polastri, D., Biassoni, V., Modena, P., Pecori, E., et al., 2013b. Relapse in medulloblastoma: what can be done after abandoning high-dose chemotherapy? A mono-institutional experience. *Childs Nerv. Syst.* [Epub ahead of print] PMID: 23595805.
- McManamy, C.S., Lamont, J.M., Taylor, R.E., Cole, M., Pearson, A.D., Clifford, S.C., et al., 2003. Morphophenotypic variation predicts clinical behavior in childhood non-desmoplastic medulloblastomas. *J. Neuropathol. Exp. Neurol.* 62 (6), 627–632.
- McManamy, C.S., Pears, J., Weston, C.L., Hanzely, Z., Ironside, J.W., Taylor, R.E., et al., 2007. Nodule formation and desmoplasia in medulloblastomas—defining the nodular/desmoplastic variant and its biological behavior. *Brain Pathol.* 17 (2), 151–164.
- Metcalfe, C., Alick, B., Crow, A., Lamoureux, M., Dijkgraaf, G.J., Peale, F., et al., 2013. PTEN loss mitigates the response of medulloblastoma to Hedgehog pathway inhibition. *Cancer Res.* 73 (23), 7034–7042.
- Min, H.S., Lee, J.Y., Kim, S.K., Park, S.H., 2013. Genetic grouping of medulloblastomas by representative markers in pathologic diagnosis. *Transl. Oncol.* 6 (3), 265–272.
- Minn, A.Y., Pollock, B.H., Garzarella, L., Dahl, G.V., Kun, L.E., Ducore, J.M., et al., 2001. Surveillance neuroimaging to detect relapse in childhood brain tumors: a Pediatric Oncology Group study. *J. Clin. Oncol.* 19 (21), 4135–4140.
- Morfouace, M., Shelat, A., Jacus, M., Freeman 3rd, B.B., Turner, D., Robinson, S., et al., 2014. Pemetrexed and gemcitabine as combination therapy for the treatment of Group3 medulloblastoma. *Cancer Cell* 25 (4), 516–529.
- Morrissey, A.S., Garzia, L., Shih, D.J., Zuyderduyn, S., Huang, X., Skowron, P., Remke, M., Cavalli, F.M., Ramaswamy, V., Lindsay, P.E., Jelveh, S., Donovan, L.K., Wang, X., Luu, B., Zayne, K., Li, Y., Mayoch, C., Thiessen, H., Mercier, E., Mungall, K.L., Ma, Y., Tse, K., Zeng, T., Shumansky, K., Roth, A.J., Shah, S., Farooq, H., Kijima, N., Holgado, B.L., Lee, J.J., Matan-Lithwick, S., Liu, J., Mack, S.C., Manno, A., Michealraj, K.A., Nor, C., Peacock, J., Qin, L., Reimand, J., Rolider, A., Thompson, Y.Y., Wu, X., Pugh, T., Ally, A., Bilenky, M., Butterfield, Y.S., Carlsen, R., Cheng, Y., Chuah, E., Corbett, R.D., Dhalla, N., He, A., Lee, D., Li, H.I., Long, W., Mayo, M., Plettner, P., Qian, J.Q., Schein, J.E., Tam, A., Wong, T., Birol, I., Zhao, Y., Faria, C.C., Pimentel, J., Nunes, S., Shalaby, T., Grotzer, M., Pollack, I.F., Hamilton, R.L., Li, X.N., Bendel, A.E., Fuets, D.W., Walter, A.W., Kumabe, T., Tominaga, T., Collins, V.P., Cho, Y.J., Hoffman, C., Lyden, D., Wisoff, J.H., Garvin Jr., J.H., Stearns, D.S., Massimi, L., Schüller, U., Sterba, J., Zitterbart, K., Puget, S., Ayrault, O., Dunn, S.E., Tirapelli, D.P., Carloti, C.G., Wheeler, H., Hallahan, A.R., Ingram, W., Macdonald, T.J., Olson, J.J., Van Meir, E.G., Lee, J.Y., Wang, K.C., et al., 2016. Divergent clonal selection dominates medulloblastoma at recurrence. *Nature* 529 (7586), 351–357.
- Mulhern, R.K., Kepner, J.L., Thomas, P.R., Armstrong, F.D., Friedman, H.S., Kun, L.E., 1998. Neuropsychologic functioning of survivors of childhood

- medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a pediatric oncology group study. *J. Clin. Oncol.* 16 (5), 1723–1728.
- Mulhern, R.K., Palmer, S.L., Reddick, W.E., Glass, J.O., Kun, L.E., Taylor, J., et al., 2001. Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. *J. Clin. Oncol.* 19 (2), 472–479.
- Mulhern, R.K., Palmer, S.L., Merchant, T.E., Wallace, D., Kokac, M., Brouwers, P., et al., 2005. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. *J. Clin. Oncol.* 23 (24), 5511–5519.
- Nandagopal, R., Laverdière, C., Mulrooney, D., Hudson, M.M., Meacham, L., 2008. Endocrine late effects of childhood cancer therapy: a report from the Children's Oncology Group. *Horm. Res.* 69 (2), 65–74.
- Nicholson, H.S., Kretschmar, C.S., Krailo, M., Bernstein, M., Kadota, R., Fort, D., et al., 2007. Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors: a report from the Children's Oncology Group. *Cancer* 110 (7), 1542–1550.
- Northcott, P.A., Jones, D.T., Kool, M., Robinson, G.W., Gilbertson, R.J., Cho, Y.J., et al., 2012. Medulloblastomics: the end of the beginning. *Nat. Rev. Cancer* 12 (12), 818–834.
- Odame, I., Duckworth, J., Talsma, D., Beaumont, L., Furlong, W., Webber, C., et al., 2006. Osteopenia: physical activity and health-related quality of life in survivors of brain tumors treated in childhood. *Pediatr. Blood Cancer* 46 (3), 357–362.
- Packer, R.J., Siegel, K.R., Sutton, L.N., Evans, A.E., D'Angio, G., Rorke, L.B., et al., 1988. Efficacy of adjuvant chemotherapy for patients with poor-risk medulloblastoma: a preliminary report. *Ann. Neurol.* 24 (4), 503–508.
- Packer, R.J., Rood, B.R., MacDonald, T.J., 2003a. Medulloblastoma: present concepts of stratification into risk groups. *Pediatr. Neurosurg.* 39 (2), 60–67.
- Packer, R.J., Gurney, J.G., Punyko, J.A., Donaldson, S.S., Inskip, P.D., Stovall, M., et al., 2003b. Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study. *J. Clin. Oncol.* 21 (17), 3255–3261.
- Packer, R.J., Gajjar, A., Vezina, G., Rorke-Adams, L., Burger, P.C., Robertson, P.L., et al., 2006. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J. Clin. Oncol.* 24 (25), 4202–4208.
- Packer, R.J., 1990. Chemotherapy for medulloblastoma/primitive neuroectodermal tumors of the posterior fossa. *Ann. Neurol.* 28 (6), 823–828.
- Palmer, S.L., Reddick, W.E., Gajjar, A., 2007. Understanding the cognitive impact on children who are treated for medulloblastoma. *J. Pediatr. Psychol.* 32 (9), 1040–1049.
- Palmer, S.L., 2008. Neurodevelopmental impact on children treated for medulloblastoma: a review and proposed conceptual model. *Dev. Disabil. Res. Rev.* 14 (3), 203–210.
- Papo, I., Caruselli, G., Luongo, A., 1982. External ventricular drainage in the management of posterior fossa tumors in children and adolescents. *Neurosurgery* 10, 13–15.
- Pei, Y., Moore, C.E., Wang, J., Tewari, A.K., Eroshkin, A., Cho, Y.J., et al., 2012. An animal model of MYC-driven medulloblastoma. *Cancer Cell* 21 (2), 155–167.
- Peris-Bonet, R., Martinez-Garcia, C., Lacour, B., Petrovich, S., Giner-Ripoll, B., Navajas, A., et al., 2006. Childhood central nervous system tumours – incidence and survival in Europe (1978–1997): report from automated childhood cancer information system project. *Eur. J. Cancer* 42 (13), 2064–2080.
- Perreault, S., Ramaswamy, V., Achrol, A.S., Chao, K., Liu, T.T., Shih, D., Remke, M., Schubert, S., Bouffet, E., Fisher, P.G., Partap, S., Vogel, H., Taylor, M.D., Cho, Y.J., Yeom, K.W., 2014. MRI surrogates for molecular subgroups of medulloblastoma. *AJNR Am. J. Neuroradiol.* 35 (7), 1263–1269.
- Peyrl, A., Chocholous, M., Kieran, M.W., Azizi, A.A., Prucker, C., Czech, T., et al., 2012. Antiangiogenic metronomic therapy for children with recurrent embryonal brain tumors. *Pediatr. Blood Cancer* 59 (3), 511–517.
- Pizer, B., Donachie, P.H., Robinson, K., Taylor, R.E., Michalski, A., Punt, J., et al., 2011. Treatment of recurrent central nervous system primitive neuroectodermal tumours in children and adolescents: results of a Children's Cancer and Leukaemia Group study. *Eur. J. Cancer* 47 (9), 1389–1397.
- Pogoda, J.M., Preston-Martin, S., Howe, G., Lubin, F., Mueller, B.A., Holly, E.A., et al., 2009. An international case-control study of maternal diet during pregnancy and childhood brain tumor risk: a histology-specific analysis by food group. *Ann. Epidemiol.* 19 (3), 148–160.
- RARECAREnet Available at, <http://www.rarecarenet.eu/rarecarenet/>.
- Reeves, C.B., Palmer, S.L., Reddick, W.E., Merchant, T.E., Buchanan, G.M., Gajjar, A., et al., 2006. Attention and memory functioning among pediatric patients with medulloblastoma. *J. Pediatr. Psychol.* 31 (3), 272–280.
- Ridola, V., Grill, J., Doz, F., Gentet, J.C., Frappaz, D., Raquin, M.A., et al., 2007. High-dose chemotherapy with autologous stem cell rescue followed by posterior fossa irradiation for local medulloblastoma recurrence or progression after conventional chemotherapy. *Cancer* 110 (1), 156–163.
- Robertson, P.L., Muraszko, K.M., Holmes, E.J., Spoto, R., Packer, R.J., Gajjar, A., et al., 2006. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. *J. Neurosurg.* 105 (Suppl. 6), 444–451.
- Rose, S.R., Danish, R.K., Kearney, N.S., Schreiber, R.E., Lustig, R.H., Burghen, G.A., Hudson, M.M., 2005. ACTH deficiency in childhood cancer survivors. *Pediatr. Blood Cancer* 45 (6), 808–813.
- Rose, S.R., 2003. Endocrinopathies in childhood cancer survivors. *Endocrinologist* 13, 488–495.
- Rosso, A.L., Hovinga, M.E., Rorke-Adams, L.B., Spector, L.G., Bunin, G.R., 2008. Children's Oncology Group. A case-control study of childhood brain tumors and fathers' hobbies: a Children's Oncology Group study. *Cancer Causes Control* 19 (10), 1201–1207.
- Rutkowski, S., Bode, U., Deinlein, F., Ottensmeier, H., Warmuth-Metz, M., Soerensen, N., et al., 2005. Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. *N. Engl. J. Med.* 352 (10), 978–986.
- Rutkowski, S., Gerber, N.U., von Hoff, K., Gnekow, A., Bode, U., Graf, N., et al., 2009. Treatment of early childhood medulloblastoma by postoperative chemotherapy and deferred radiotherapy. *Neuro Oncol.* 11 (2), 201–210.
- Rutkowski, S., von Hoff, K., Emser, A., Zwiener, I., Pietsch, T., Figarella-Branger, D., et al., 2010. Survival and prognostic factors of early childhood medulloblastoma: an international meta-analysis. *J. Clin. Oncol.* 28 (33), 4961–4968.
- Rutter, M.M., Rose, S.R., 2007. Long-term endocrine sequelae of childhood cancer. *Curr. Opin. Pediatr.* 19 (4), 480–487.
- Salaroli, R., Ronchi, A., Buttarelli, F.R., Cortesi, F., Marchese, V., Della Bella, E., et al., 2015. Wnt activation affects proliferation: invasiveness and radiosensitivity in medulloblastoma. *J. Neurooncol.* 121 (1), 119–127.
- Saran, F., Baumert, B.G., Creak, A.L., Warrington, A.P., Ashley, S., Traish, D., et al., 2008. Hypofractionated stereotactic radiotherapy in the management of recurrent or residual MB/PNET. *Pediatr. Blood Cancer* 50 (3), 554–560.
- Shih, D.J., Northcott, P.A., Remke, M., Korshunov, A., Ramaswamy, V., Kool, M., et al., 2014. Cytogenetic prognostication within medulloblastoma subgroups. *J. Clin. Oncol.* 32 (9), 886–896.
- Shim, Y.K., Mlynarek, S.P., van Wijngaarden, E., 2009. Parental exposure to pesticides and childhood brain cancer: u: S. Atlantic coast childhood brain cancer study. *Environ. Health Perspect.* 117 (6), 1002–1006.
- Shou, Y., Robinson, D.M., Amakye, D.D., Rose, K.L., Cho, Y.J., Ligon, K.L., et al., 2015. A five-gene hedgehog signature developed as a patient preselection tool for hedgehog inhibitor therapy in medulloblastoma. *Clin. Cancer Res.* 21 (3), 585–593.
- Sklar, C.A., Mertens, A.C., Mitby, P., Occhiogrosso, G., Qin, J., Heller, G., et al., 2002. Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. *J. Clin. Endocrinol. Metab.* 87 (7), 3136–3141.
- Skowron, P., Ramaswamy, V., Taylor, M.D., 2015. Genetic and molecular alterations across medulloblastoma subgroups. *J. Mol. Med. (Berl)*. 93 (10), 1075–1084.
- Strother, D., Ashley, D., Kellie, S.J., Patel, A., Jones-Wallace, D., Thompson, S., et al., 2001. Feasibility of four consecutive high-dose chemotherapy cycles with stem-cell rescue for patients with newly diagnosed medulloblastoma or supratentorial primitive neuroectodermal tumor after craniospinal radiotherapy: results of a collaborative study. *J. Clin. Oncol.* 19 (10), 2696–2704.
- Tait, D.M., Thornton-Jones, H., Bloom, H.J., Lemerle, J., Morris-Jones, P., 1990. Adjuvant chemotherapy for medulloblastoma: the first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I). *Eur. J. Cancer* 26 (4), 464–469.
- Tamburrini, G., Frassanito, P., Chieffo, D., Massimi, L., Caldarelli, M., Di Rocco, C., 2015. Cerebellar mutism. *Childs Nerv. Syst.* 31 (October (10)), 1841–1851, <http://dx.doi.org/10.1007/s00381-015-2803-6>, Epub 2015 Sep 9.
- Taylor, R.E., Bailey, C.C., Robinson, K.J., Weston, C.L., Walker, D.A., Ellison, D., et al., 2005. Outcome for patients with metastatic (M2–3) medulloblastoma treated with SIOP/UKCCSG PNET-3 chemotherapy. *Eur. J. Cancer* 41 (5), 727–734.
- Taylor, M.D., Northcott, P.A., Korshunov, A., Remke, M., Cho, Y.J., Clifford, S.C., et al., 2012. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol.* 123 (4), 465–472.
- Toogood, A.A., 2004. Endocrine consequences of brain irradiation. *Growth Horm. IGF Res.* 14 (Suppl. A), S118–S124.
- Verlooy, J., Mosseri, V., Bracard, S., Tubiana, A.L., Kalifa, C., Pichon, F., et al., 2006. Treatment of high risk medulloblastoma in children above the age of 3 years: a SFOP study. *Eur. J. Cancer* 42 (17), 3004–3014.
- Villani, A., Malkin, D., Tabori, U., 2012. Syndromes predisposing to pediatric central nervous system tumors: lessons learned and new promises. *Curr. Neurol. Neurosci. Rep.* 12 (2), 153–164.
- von Bueren, A.O., von Hoff, K., Pietsch, T., Gerber, N.U., Warmuth-Metz, M., Deinlein, F., Zwiener, I., Faldum, A., Fleischhack, G., Benesch, M., Krauss, J., Kuehl, J., Kortmann, R.D., Rutkowski, S., 2011. Treatment of young children with localized medulloblastoma by chemotherapy alone: results of the prospective, multicenter trial HIT 2000 confirming the prognostic impact of histology. *Neuro Oncol.* 13, 669–679.
- Yauch, R.L., Dijkgraaf, G.J., Aliche, B., Januario, T., Ahn, C.P., Holcomb, T., et al., 2009. Smoothed mutation confers resistance to a Hedgehog pathway inhibitor in medulloblastoma. *Science* 326 (5952), 572–574.
- Yeom, K.W., Mobley, B.C., Lober, R.M., Andre, J.B., Partap, S., Vogel, H., Barnes, P.D., 2013. Distinctive MRI features of pediatric medulloblastoma subtypes. *AJR Am. J. Roentgenol.* 200 (4), 895–903.
- Zeltzer, P.M., Boyett, J.M., Finlay, J.L., Albright, A.L., Rorke, L.B., Milstein, J.M., et al., 1999. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. *J. Clin. Oncol.* 17 (3), 832–845.
- Zhukova, N., Ramaswamy, V., Remke, M., Pfaff, E., Shih, D.J., Martin, D.C., et al., 2013. Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. *J. Clin. Oncol.* 31 (23), 2927–2935.