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European standard clinical practice recommendations for paediatric high-grade gliomas

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ABSTRACT

Paediatric high-grade gliomas (pedHGGs) are highly invasive brain tumours accounting for approximately 15 % of all central nervous system (CNS) tumours in children and adolescents. The outcome for these tumours is generally poor with 5-year survival rates of less than 20 %. Despite improved biological insights into pedHGGs and the promise of more effective therapies, little progress has been made in the effective treatment and the outcome of these tumours over the last four decades. Much of the evidence for the use of chemotherapy in pedHGGs is extrapolated from adult data, and the evidence for its use in the paediatric population is still weak. This guideline was written by members of the SIOPE HGG Working Group as part of the European Standard Clinical Practice (ESCP) Project of the European Reference Network for Paediatric Oncology, ERN PaedCan. The guideline aims to integrate available evidence-based and expert opinion-based information to assist healthcare professionals in the management of pedHGGs and in an attempt to provide equity in healthcare reflecting the varying resources of each European country.

1. Introduction

Paediatric high-grade gliomas (pedHGGs) are highly invasive brain tumours accounting for approximately 15 % of all central nervous system (CNS) tumours in children and adolescents. The outcome for these tumours is generally poor with 5-year survival rates of less than 20 % [1]. They represent significantly different biology compared to their adult counterparts, and it is now understood that they represent a heterogeneous group of tumours rather than just one entity, a fact that has recently been further acknowledged in the 5th edition of the 2021 WHO CNS tumour classification [1,2].

Despite the historical existence of a significant number of prospective clinical trials for children with pedHGGs, there has been little improvement in patient outcomes over the past 4 decades. Until now, following surgery and adjuvant radiotherapy, temozolomide-containing regimens have been standard practice among paediatric neuro-oncologists, and also used as a control arm in clinical trials, with most care providers aiming to ultimately enrol pedHGG patients into investigational clinical trials [3–5].

The general challenges for the design of early clinical trials in pedHGGs are 4-fold: intertumoural heterogeneity and molecular pathway redundancy; lack of currently actionable alterations in a large proportion of patients; small subsets of patients for each given biology and target expression; issues with drug delivery due to poor blood–brain barrier penetration [6].

This guideline was written by members of the SIOPE HGG Working Group as part of the European Standard Clinical Practice (ESCP) Project. The guideline was reviewed by board members of the European Reference Networks (ERNs) and the European Society for Paediatric Oncology (SIOPE) and finally approved for publication in the SIOPE members' portal, exclusive to SIOPE members.

As patients with pedHGGs do not have access to the same level of care in all countries, and treatment varies across different institutions, the guideline aims to integrate available evidence-based and expert opinion-based information to assist healthcare professionals in the management of pedHGGs and in an attempt to provide equity in healthcare reflecting the varying resources of each European country.

2. Classification and previous management approach

High-grade gliomas (HGGs) are aggressive tumours (defined as CNS WHO grade 3 or 4) exhibiting glial differentiation. The types of HGG seen in children can be found under several broad groups:

2.1. Diffuse midline glioma H3K27-altered

H3K27-altered diffuse midline gliomas (DMGs) represent 10 % of brain tumours and 70 % of HGGs in children. These tumours arise in the midline structures of the brain (pons, thalamus, spinal cord). Most tumours carry a variant in H3K27 resulting in loss of H3K27 trimethylation (H3K27me3), and this genetic mark is associated with a uniformly fatal disease course, independent of tumour location [7,8]. H3K27-altered DMGs were acknowledged as a new entity in the WHO 2016 classification and have been subdivided in the recent 2021 classification into different subtypes: a predominant group presenting histone H3 mutations (H3.3 p.K28M (K27M)-mutant, and H3.1 or 3.2 p.K28M (K27M)-mutant), often associated with *PDGFRA* and *MYC* amplifications [2]. A smaller group of DMG lack H3 mutation, rather show global epigenetic changes consistent with mutant through EZHIP overexpression [2,9]. Furthermore, an additional group with H3K27me3 loss and frequent *EGFR* gene alterations has been described [10]. All *H3K27*-altered DMGs share Polycomb Repressor Complex 2 (PRC2) inhibition and are therefore classified together in the WHO classification 2021 [11]. A small subgroup of HGGs that occur in the midline showing amplification of *MYCN* (*GBM-MYCN*) is now re-classified separately within the group of diffuse paediatric-type HGG, H3-wildtype, and IDH-wildtype, subgroup pedHGG MYCN [2,12].

DMGs have historically been treated in the same way as hemispheric gliomas, although the Children's Oncology Group (COG) study ACNS-0126 of temozolomide (TMZ) adjuvant to RT (TMZ-RT) in hemispheric pedHGGs and DMGs concluded that there is little justification for using TMZ in DIPG (now known as pontine DMG) [13]. The study by Cohen *et al.* was not randomized to radiotherapy only but showed TMZ-RT not to be inferior/superior to the preceding CCG-9941 study that employed intensive pre-radiation chemotherapy and hyper-fractionation. Interestingly, a large analysis of 1130 DIPG patients by the SIOPE and International DIPG registries revealed that any neo-adjuvant or adjuvant systemic therapy (mostly TMZ-based) in addition to radiotherapy (RT) correlated with longer survival in both univariable and multivariable analyses. This had also previously been observed in retrospective analyses by Wagner *et al.* where a better median overall survival (OS) (11.3 months) was observed in DIPG patients treated with adjuvant chemotherapy following RT compared with patients treated with RT alone (9.5 months; $P = 0.03$) [14]. Likewise, in a retrospective analysis by Kebudi *et al.* patients receiving adjuvant TMZ or other chemotherapy (lomustine, vincristine) after RT, had a significantly higher survival than those treated with RT only [15]. This has also been shown in other studies using neo-adjuvant intensive chemotherapy [14–17]. However, none of these studies address a well-defined H3K27-altered DMG subgroup and, as non-randomized studies, might be subject to bias. In the Herby randomized trial for non-brainstem midline pedHGGs, survival with *H3K27M-mutation* was equally poor (8.0 months OS) with no superiority of bevacizumab added to TMZ-RT [5,18]. In 2014, an adaptive design protocol (BIOMEDE 1.0 trial) was developed for DMGs *H3K27*-altered. In this study, most patients received a treatment assumed to specifically target a biological abnormality identified on the biopsy. The three drugs administered were erlotinib, dasatinib and everolimus (NCT02233049). None of these targeted agents was shown to be superior to the other, with a median OS of 10.0, 10.5 and 11.9 months, respectively [19]. Everolimus was chosen

as a 'standard arm' for the subsequent BIOMEDE 2.0 trial because of fewer side effects [7].

Both, the SIOPE and International Diffuse Intrinsic Pontine Glioma Registries (https://dipgregistry.eu and https://dipgregistry.org) created in 2012 have made a major contribution towards understanding this challenging disease and have been broadened to all DMGs in 2022 and 2019, respectively. The registries ensure prospective data collection and help develop new approaches to treating DMGs.

2.2. Hemispheric pedHGGs

Hemispheric pedHGGs represent 5 % of brain tumours and 30 % of HGGs in children. These include H3G34R/V diffuse hemispheric glioma, paediatric-type high-grade glioma and infant-type high-grade glioma, as classified in the 2021 WHO classification of CNS tumours. From the United States, the first prospective, randomized clinical trial, CCG-943, for children with HGG was published in 1989 by the Children's Cancer Study Group (CCG) and showed a significant improvement in outcome of radiotherapy followed by prednisolone/chloroethyl-cyclohexyl nitrosourea [lomustine]/vincristine chemotherapy (PCV), over radiotherapy alone, after maximal safe surgery [20]. Five-year OS rates of 43 % (± 9 %) and 17 % (± 7 %) were reported for RT/PCV vs RT, respectively. In the follow-up RCT CCG-945 study, the RT/PCV regimen was compared to eight-drugs-in-1-day (8-in-1) chemotherapy with no significant difference between the arms, with a 5-year OS of 36 % (± 6 %) [21]. Gross total resection (>90 %) was found to be an important prognostic marker for survival. Overexpression of O^6-DNA methylguanine-methyltransferase (*MGMT*) was strongly correlated with adverse outcomes in both arms of the CCG-945 study [22]. Of note, a later central review of the pathology of the CCG-945 study indicated that 30 % of patients were low-grade gliomas misclassified as HGGs, resulting in an adjusted OS rate of 22 % (± 3 %) for HGG in CCG-945 [23]. Unfortunately, this neuropathological reanalysis was not performed for the CCG-943 study.

In a pivotal trial (2000–2002), the alkylating agent TMZ was introduced in adult glioblastoma patients. Single-agent TMZ, when administered during and after RT, significantly prolonged event-free survivals (EFS) and OS in adults with glioblastoma compared with RT alone [24]. While methylation of the *MGMT* promoter was confirmed as a prognostic marker, the predictive value for benefit from TMZ has not been prospectively demonstrated for paediatric patients as in the adult setting [25,26]. In analogy to the experience with TMZ in adults, the COG study ACNS0126 employed TMZ concurrently with RT and showed an equal survival outcome to the previous CCG-945 study, with a 3-year EFS and OS of 11 ± 7 % and 22 % ± 5 %, respectively. TMZ treatment showed less toxicity compared to previous CCG trials [13]. The role of lomustine added to TMZ was investigated in the subsequent ACNS-0423 study that resulted in better 3-year EFS and OS rates of 22 ± 8 % and 28 ± 8 % respectively, most pronounced for patients with methylation of the MGMT promoter and non-GTR patients however, at the expense of increased toxicity [27]. Likewise, in adult GBM patients with *MGMT* promoter methylated tumours, the CeTeG/NOA-09 study (NCT01149109) showed TMZ combined with lomustine to be superior to TMZ alone [28]. This study was performed in a selected group of *MGMT-methylated* patients, as a prior pilot study had indicated that no benefit of adding lomustine to TMZ was observed in MGMT-unmethylated, MGMT-expressing tumours [29]. In contrast, another non-randomised phase 2 trial (UKT-03) suggested lomustine -TMZ plus RT to be superior to temozolomide chemoradiotherapy in newly diagnosed glioblastoma with methylation of the MGMT promoter (MGMTp). However, the previous paediatric trial HIT-HGG-2007 showed that only 8 out of 183 (4.4 %) patients had a confirmed MGMTp hypermethylated tumour and only 22 out of 183 (12.0 %) patients had a moderately methylated MGMTp. The majority (83.6 %) of pedHGGs showed an unmethylated MGMTp, which did not affect survival in the setting of TMZ-RT-based therapy. This suggests that, unlike in adult patients, MGMTp methylation status in children is not associated with survival outcome (Christof Kramm, paper submitted).

The most recent COG HGG trial, ACNS0822, compared two different experimental arms with vorinostat or bevacizumab during RT with a control arm with TMZ during RT. The study was initially planned as a "pick-the-winner" phase II design to be advanced into phase III testing, but the study was permanently closed in 2014 during phase II, as no arm showed any clear superiority over TMZ/RT [30]. The addition of bevacizumab to a backbone of TMZ/RT (Herby trial) failed to improve EFS and OS in non-brainstem pedHGGs *[5]*. Post-hoc analyses of the molecular characteristics of the patients included in this trial, however, seem to indicate that the addition of bevacizumab might provide some benefit to certain subgroups of pedHGGs, including hypermutated and BRAF-V600E mutated pedHGGs [18].

The use of pre-irradiation chemotherapy has been evaluated in a phase II approach, where 4 courses of neo-adjuvant ifosfamide, carboplatin, and etoposide (ICE) chemotherapy were given followed by hyperfractionated RT (1.1 Gy twice daily for 30 days) and 4 courses of ICE adjuvant therapy. This study showed low toxicity and 5-year progression-free survival (PFS) of 56 % and OS of 67 %. Brainstem tumours in this study did not benefit from this approach [31]. Furthermore, in patients with pedHGGs treated on the German HIT-GBM-C cooperative group study with intensive chemotherapy during and after RT (cisplatin, etoposide, and weekly vincristine during radio-chemotherapy, with one cycle of cisplatin, etoposide, and ifosfamide during the last week of radiation, and subsequent maintenance chemotherapy followed by oral valproic acid), survival was better than that seen in prior HIT-GBM studies in the subgroup of patients with HGG who had undergone gross total resection (5-year OS rate 63 % vs 17 % for the historical control group, $P = .003$, log-rank test). Molecular data were not provided, however, rendering the data difficult to interpret [32].

The German cooperative group is currently conducting the HIT-HGG-2013 trial (DRKS-ID:DRKS00012806) comparing the combination of TMZ and valproate with historical data from their previous studies, HIT-HGG-2007 (NCT03243461), using single agent TMZ.

Other studies are exploring the role of an immune checkpoint inhibitor, nivolumab, in management of HGGs, i.e. the French NIVOGLIO phase I/II trial is investigating the combination of nivolumab with TMZ and radiotherapy in children and adolescents with newly diagnosed HGG (NCT04267146).

2.3. Infant-type hemispheric HGG

Infants with HGG have long been known to show better survival compared with older children and an improved outcome both with chemotherapy after surgery and, if necessary, delayed radiotherapy. Infants with malignant astrocytoma treated with the 8-in-1 regimen used in the CCG-945 study were reported to have a 3-year PFS and OS of 36 % and 51 % respectively, markedly better than older children treated with this regimen in combination with RT [33]. In parallel, from 1986 to 1996, the Baby POG I study reported cases cured with 24 months of chemotherapy alone using prolonged alternating chemotherapy consisting of two cycles of cyclophosphamide and vincristine followed by a third cycle of cisplatin and etoposide. The study reported 5-year PFS and OS of 43 % and 50 % for the 18 pedHGG patients [34]. With the French chemotherapy-only BBSFOP protocol, an 18-month schedule of seven cycles of three drug pairs (carboplatin-procarbazine, cisplatin-etoposide and vincristine-cyclophosphamide) in pedHGG patients under the age of 5 years, a 5-year PFS of 35.3 % and OS of 58.8 % were observed [34]. In the UKCCSG/SIOP CNS 9204 trial, infants with non-brainstem HGG were treated with courses of carboplatin/vincristine, high-dose methotrexate/vincristine, cyclophosphamide monotherapy and cisplatin monotherapy, resulting in PFS and OS rates of 13.0 % and 30.9 % [35].

There has been emerging evidence that different biology may be a major contributing factor to the survival differences between infant and

paediatric HGGs. A large proportion of infant patients, especially those *under 2 years of age*, were shown to have tumours molecularly distinct from those in older children, and the group 'Infant-type hemispheric glioma' is now recognized in WHO CNS 2021. These studies also indicate a role for targeted therapies in this patient group, as driving targetable molecular alterations have been defined such as gene fusions involving *ALK*, *ROS1*, *NTRK1/2/3*, and *MET* [36,37].

3. Diagnostic process

3.1. Imaging

Magnetic resonance imaging (MRI) is the mainstay for a comprehensive evaluation of the neuroaxis, and it is vital to include the whole brain and spine at baseline and in case of suspected progression.

Recommendations on essential MRI sequences for brain and spine imaging, tumour measurement, post-operative residual tumour definitions and response criteria are included in the SIOPE MRI guidelines for imaging patients with CNS tumours and in the Standard Clinical Practice Recommendations published by the Imaging Working Group [38,39].

3.2. Role of CSF analysis

CSF collection is not routinely performed for pedHGGs. It may become relevant in the context of liquid biopsies, but currently, this is not the standard.

3.3. Biopsy in pontine DMGs

The diagnosis of pontine DMG (pDMG) is conventionally made based on the combination of a typical clinical presentation and the well-described radiological findings on MRI. Tumour tissue is not considered necessary for diagnosis and management unless there are atypical features with respect to patient age, presenting signs and symptoms, duration of symptoms, or neuroradiological appearances. Over the years, this has led to considerable debate among neurosurgeons and oncologists [40,41]. The paucity of biological tissue accounts for the poor understanding of the molecular biology of pDMGs, and potentially the lack of therapeutic progress, relative to other tumours [42].

Several studies have shown that biopsy of pDMG is safe in experienced hands [42–44]. A large meta-analysis evaluated 735 biopsy procedures in paediatric brainstem tumours and found an overall diagnostic success rate of 96.1 %; the rates for permanent morbidity and mortality were both only 0.6 % [44]. Surgical adjuncts such as navigational robotic technology increase accuracy and safety [45,46].

In studies such as BIOMEDE and INFORM, biopsy was mandatory, and the tumour tissue obtained yielded sufficient material for detailed molecular investigation, with very low rates of adverse events [47,48].

It is hoped that as new clinical trials and potential therapeutic options emerge, the value of biopsy in identifying the molecular subgroups, defining prognosis, and assessing trial eligibility will be reappraised [49]. It is now accepted that for most clinical trials a biopsy will be requested for suspected pDMG as per the study protocol since the procedure is now widely disseminated in many neuro-oncology centres without life-threatening complications.

Outside of a clinical trial when a diagnosis of DMG can be based on typical neuroradiological imaging appearances, biopsy can be considered following discussion with families about relative benefits of confirmatory histopathology, possible molecular targeting given emerging evidence for prolonged PFS/OS in some subgroups of DMG, and possible future research applications of left over tissue sample. In those circumstances when atypical tumour appearances are present on images, a biopsy is recommended.

3.4. Neuropathological diagnosis

For the exact classification of pedHGGs and the exclusion of histological mimics, the diagnostic methodology should include immunohistochemical assessment of cell lineage and surrogate protein markers for genetic alterations (including immunohistochemistry with antibodies against mutant proteins and epigenetic histone marks) as well as molecular pathological techniques to identify genetic alterations on DNA and/or RNA level and to establish epigenetic profiles for methylation-based tumour classification. Most pedHGG entities are defined by the presence/absence of specific genetic alterations and can also be identified by their *characteristic methylation profiles*.

Histology	**DIFFUSE HIGH-GRADE GLIOMA**				
Location	Hemispheric			Midline	Any
Age group	Adolescents	Adolescents	Infants < 2 years	(Pre)school children	(Pre)school children
IDH status	IDH-wildtype	IDH-mutant	IDH-wildtype	IDH-wildtype	IDH-wildtype
Histone 3 status	H3.3 G34R/V	H3-wildtype	H3-wildtype	**H3 K27me3 loss:** H3.3 K27M/K27I mutant or H3.1/H3.2 K27M mutant or EZHIP overexpression or *EGFR* altered (see below)	H3-wildtype
RTK status	PDGFRA mutation/ amplification		*ALK* or *ROS1* or *NTRK1–3* or *MET* fusion	*EGFR* ex20ins mutation or other *EGFR* alterations (mostly in thalamic/ EZHIP cases)	PDGFRA/EGFR/MET amplification
Mismatch repair status (if MMR deficiency suspected)	No PMS2, MLH1, MSH2, MSH6 IHC loss	No PMS2, MLH1, MSH2, MSH6 IHC loss PMMRDIA	No PMS2, MLH1, MSH2, MSH6 IHC loss	No PMS2, MLH1, MSH2, MSH6 IHC loss	MMR associated HGG: loss of expression of at least one of mismatch repair proteins
Methylome	Distinct profile	Distinct profile	Distinct methylome profile, also for non-ALK/ROS/MET-NTRK cases	Can help detect EZHIP OE DMGs	For further subtyping (pedRTK1, pedRTK2, MYCN)
Integrated diagnosis	Diffuse hemispheric glioma, H3 G34-mutant, CNS WHO grade 4	Astrocytoma IDH-mutant CNS WHO grade 3/4	Infant-type hemispheric glioma, H3-wildtype and IDH-wildtype, No CNS WHO grade	Diffuse midline glioma, H3 K27-altered, CNS WHO grade 4	Diffuse pediatric-type HGG, H3-wildtype and IDH-wildtype, CNS WHO grade 4

The following algorithm based on WHO CNS 2021 may help to further molecularly characterize pedHGGs [2, 7, 50, 51]:

Additional molecular tests become necessary for other glioma types that enter the differential diagnosis of pedHGGs. Examples are "adult-type" IDH-mutant astrocytomas which can also occur in older children/adolescents and pleomorphic xanthoastrocytoma for which diagnostic testing for homozygous *CDKN2AB* deletions and *BRAF*V600E and other MAP kinase alterations are recommended. DNA methylation profiling adds an important layer of information to confirm neuropathological diagnoses, provide information on subtypes of H3- and IDH-wildtype HGG, and identify molecular or histological mimics of pedHGGs.

In infant-type hemispheric gliomas (but also in other pedHGG subtypes), appropriate RNA-and/or DNA-based analysis for specific *gene fusions* (i.e., *ALK, ROS1, MET, NTRK* family) may help to identify possible candidates for targeted therapy.

Molecular/immunohistochemical assessment of mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or assessment of tumour mutational burden (TMB) may help to identify patients with (germline) mismatch repair deficiency, which could indicate a rationale for immune checkpoint inhibitor treatment. We recommend the use of IHC for the MMR genes in cases with clinical suspicion of a constitutional mismatch repair deficiency syndrome (CMMRD) [51], which may also include IDH mutant pedHGG.

High-grade IDH-WT diffuse glioma may occur in children with Li-Fraumeni syndrome [52].

Where adequate molecular testing is not available to determine the type of pedHGG, the term 'High-grade gliomas, NOS' should be used.

4. Treatment

Management of pedHGGs in the context of cancer predisposition syndromes is outside of the scope of this guideline but will be addressed in the first revision of this guideline in view of the emerging evidence that these patients benefit from immunotherapy.

4.1. Surgery

The goal of surgery in hemispheric pedHGGs is to achieve a maximal resection whenever possible without causing lasting and disabling neurological deficits. Experience from adult HGG suggests that gross total resections increase PFS [53,54]. If tumours are widespread or localised in eloquent non-operable regions of the brain such as pons, a biopsy is recommended to verify histologic and molecular genetic diagnostics, which can be achieved by microsurgery, neuroendoscopy, or navigated, stereotactic or robotic needle biopsy. The surgical strategy follows basic techniques for resection. Advances in surgery are primarily related to technical developments that facilitate maximal safe resection, i.e. intraoperative MRI, intraoperative ultrasound and 5-ALA fluorescence-guided surgery [55,56]. Awake surgery is difficult in the paediatric population but in selected cases it could be used to increase safety when operating near eloquent areas [57].

4.2. Corticosteroids

Corticosteroids are commonly used in children with symptomatic CNS tumours [58]. The benefit of corticosteroids is recognized in case of raised ICP and in preparation to surgery, under radiotherapy and in long term palliative symptomatic treatment, but their use should be restricted as corticosteroids reduce the permeability of the blood-brain barrier and might impair the anti-tumour immunity [59].

4.3. Radiotherapy

4.3.1. Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype and Diffuse hemispheric glioma H3 G34-mutant [5,20,21,27,60–62]

The optimal dose and volume of irradiation have never been studied prospectively or retrospectively. In the past, recommendations for radiotherapy were based on adult experience despite different radiological presentation, biology, and outcomes.

After maximal safe surgery, a delay of less than 4–6 weeks is recommended before the start of radiation therapy [63].

Dose:

- According to multi-institutional studies, local radiotherapy is proposed for patients ≥ 3 years, with a dose of 54 Gy +/- a boost of 5,4 Gy (1,8 Gy/fraction) to residual disease [64].
- In the case of Intensity Modulated Radiation Therapy, a simultaneous boost can be proposed to optimize the dose to healthy tissue (54 Gy/1,8 by fraction and 60 Gy/2 Gy by fraction).

Target Volume [65]:

- Regarding irradiation volume, Gross Total Volume (GTV) is defined as surgical cavity plus postoperative residual disease on T1-contrast (or T2 Flair for non-enhanced tumours).
- Clinical Total Volume (CTV) is GTV plus a margin of 15 mm limited by natural anatomic barrier. In the case of a non-enhancing tumour, the CTV margin could be reduced to 10 mm.
- Planning Target Volume (PTV) is CTV plus geometric expansion of 2–5 mm according to institutional policy.

Data regarding re-irradiation in patients with non-pontine DMG are scarce. Retrospective data suggest that re-irradiation is safe and can offer good palliation of symptoms. Optimal dose, fractionation dose and volume are unknown [66,67].

In adults, a median dose of 35 Gy in 10 fractions in association with bevacizumab has been shown to be safe but without improvement in survival. Another retrospective study from Combs *et al.* has shown similar results with 36 Gy (2 Gy/fraction) in stereotactic conditions. In these reports, the target volume is defined as GTV plus a margin for PTV [66, 68, 69].

4.3.2. Diffuse midline glioma H3K27-altered

In childhood, diffuse midline gliomas *H3K27*-altered (DMGs) are mainly located in the pons followed by thalamic location and rarely in the spinal cord.

For **non-pontine DMG**, limited data are available about specific treatments. Currently, recommendations for radiation therapy are the same as for other diffuse paediatric-type high-grade gliomas.

For **pontine DMG**, the recommendations are as follows:

Although rapid initiation of radiation therapy is desirable, the 'optimal delay' (if needed) between diagnosis and the start of radiotherapy is unknown. Short delay (within 2 weeks) does not improve overall survival [63,70].

Dose and fractionation:

- The standard dose of radiation therapy is 54 Gy in 1,8 Gy by fraction (5 fractions a week) for all DMG.
- For patients with pontine DMG, hypofractionated treatment is proven to be non-inferior to conventional fractionation [71–76]. The most used scheme is 39 Gy in 13 fractions (3 Gy/fraction in 2,5 weeks) without concomitant systemic therapy. Hypofractinated radiotherapy is an option to reduce the treatment burden in children particularly those with Lansky scale of 50–70 with significant neurological symptoms such as pyramidal tract dysfunction or disequilibrium.

- There is no role of hyperfractionated radiotherapy in the management of diffuse intrinsic pontine glioma [7, 77, 78].

Target volume [79]:

- GTV is defined by a combination of the T1-contrast, T2 and Flair abnormality.
- CTV include GTV plus a margin of 10 mm limited by natural anatomic barriers such as bony calvarium and tentorium.
- PTV is CTV plus geometric expansion of 2–5 mm according to institutional policy.

Re-irradiation of pontine DMG (pDMG) [67, 69, 80, 81–86]

There is evidence that re-irradiation in pDMG patients improves survival and symptoms in more than 2/3 of patients. The best candidates are patients with a response to initial treatment and after at least 3 months since the first irradiation course.

Dose: Re-irradiation dose, volume and fractionation are variable according to the different institutions. Some data suggest that $\geq$ 20 Gy (1,8–2 Gy/fraction) is slightly more effective in terms of symptom improvement. More data is needed to determine if a dose up to 36 Gy could offer additional benefit.

Target Volume: PTV is usually GTV plus a margin of 2–5 mm with a limited margin for CTV, at the discretion of the radiation oncologist, in the absence of consensus.

4.3.3. *Infant–type hemispheric glioma*

Age

For the infant subgroup, we chose the age cut-off of 2 years in these guidelines, based on the neuropathological diagnosis even though the treatment age groups are usually defined with an age cut-off of 3 years [36,37].

Infant HGG is usually managed with surgery and systemic treatment (chemotherapy and/or target therapy). Radiation therapy is rarely considered in the treatment strategy considering the severe late effects in infants. Radiotherapy is an option for relapse in selected cases (according to patient age, the previous treatment and molecular subtype).

No specific recommendation is therefore available for this rare entity [34, 35, 86–90].

4.3.4. *Spinal cord high-grade glioma [27,85,91,92]*

High-grade glioma arising from the spinal cord is very rare in the paediatric population. *H3K27* alterations are very frequent in this location (50–80 %) [87,92–94]. The delivered radiotherapy dose is usually lower compared to intracranial tumours because of the spinal cord's tolerance to radiotherapy.

Dose: 45–50.4 Gy (1,8 Gy/fraction) according to the length of the involved spinal cord and neurological status.

Target Volume: There is no agreement, and treatment is based on experience from intracranial high-grade glioma with a CTV margin up to 20 mm in the CC direction.

4.3.5. *Metastatic DMG*

For all DMGs (including pontine), CSI (36 Gy in 20 daily fractions of 1.8 Gy) with a boost to the primary tumour and macroscopic metastases (18 Gy in 10 daily fractions) to a total dose of to 54 Gy, in case of metastatic disease at the time of diagnosis, is an option.

In case of metastatic relapse ($\geq$50 % of patients with thalamic lesions) after previous radiotherapy, a CSI of 36 Gy in 20 fractions could be offered.

5. Chemotherapy

Despite biological insight into pedHGGs and the promise of more effective therapies, little progress has been made in the effective treatment and, hence, the outcome of these tumours in the last four decades. Much of the evidence for the use of chemotherapy in pedHGGs is extrapolated from adult data, and the evidence for its use in the paediatric population is weak. To date, only a few randomised trials have been performed involving newly diagnosed pHGGs with sizeable patient numbers that have demonstrated a benefit from adjuvant chemotherapy [20,21]. Although most children receive adjuvant chemotherapy, the optimal regimen to offer patients with newly diagnosed pedHGGs has not been established.

Given there is no clear indication to support one approach over another, the SIOPE HGG Working Group conducted a pan-survey aiming to establish the current management approaches of pedHGG in Europe. Based on the practice in 33 countries, an attempt was made to achieve a consensus on the management of these tumours using a Delphi method [95]. Forty-three recognized neuro-oncology experts from 33 countries were invited to participate in the Delphi process between December 2021 and March 2022. Voting and responses were collated using a web-based survey [96].

5.1. *Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype and diffuse hemispheric glioma H3 G34-mutant*

A concomitant daily administration of temozolomide (TMZ) with local radiotherapy followed by adjuvant chemotherapy with TMZ has been widely adopted by the paediatric neuro-oncology community throughout Europe as the preferred treatment option for pedHGGs. Sixty per cent of the Delphi participants agreed that the recommended treatment regimen is chemoradiation with TMZ followed, after a TMZ treatment break of approximately 4 weeks, by 6–12 cycles of TMZ, irrespective of *MGMT* promotor methylation status.

Treatment should begin approximately 4 weeks after cranial surgery. Alternatively, after irradiation, patients should be enrolled on a clinical trial when available.

Recommended chemoradiation regimen:

1. During the chemoradiation treatment phase: Daily continuous TMZ (75 mg/m^2/d) starting concomitantly with the first radiation fraction and ending with the last radiation fraction (see details in radiotherapy section).
2. During the TMZ adjuvant treatment phase: Temozolomide (150 – 200 mg/m^2/d) x 12 cycles:

- 1st cycle 150 mg/m^2/days 1–5, escalated to 200 mg/m^2/days 1–5 from the 2nd cycle onwards depending on the tolerance during the 1st cycle
- Cycle length = 28 days

The above regimen, commonly referred to as the 'Stupp regimen', has been based on the first randomized study to demonstrate significant survival benefit when adjuvant chemotherapy was added to radiotherapy in adult patients with newly diagnosed GBM. This trial demonstrated an improvement in the median and 2-year survival, a benefit that lasted throughout 5 years of follow-up [97].

Subsequently, the efficacy, safety, and tolerability data from the completed large single-arm Phase II COG study ACNS0126 provided support for the use of radiotherapy with concomitant and adjuvant TMZ in newly diagnosed pedHGGs [13]. Although the efficacy results did not demonstrate a clear advantage of this regimen over other chemotherapy agents in subsequent trials [21,62], the favourable safety profile and excellent tolerability of this regimen have nevertheless resulted in its continued acceptance by both physicians and patients.

Thirty per cent of the Delphi participants would support the management of hemispheric HGG using concomitant and/or adjuvant TMZ as the backbone but would consider adding lomustine based on the COG ACNS-0423 trial due to the findings of the difference in survival between the cohort of patients with *MGMT*-overexpressing tumours in ACNS0126 and ACNS0423 [27]. In this trial, children with a newly diagnosed

localised pedHGG underwent radiotherapy with concurrent TMZ following maximal surgical resection. Adjuvant chemotherapy consisted of up to 6 cycles of lomustine 90 mg/m^2/day on day 1 and TMZ 160 mg/m^2/day on days 1–5 every 6 weeks. Cycles were repeated every 42 days upon bone marrow recovery [27].

The hypothesis was that the dual-alkylator regimen might help to overcome *MGMT*-mediated resistance by depleting *MGMT*. However, this remains of debate as the study was non-randomized and MGMT immunohistochemistry is controversial in comparison to the *MGMT* methylation status. Moreover, the significance of *MGMT* expression in predicting response to alkylating agents in pedHGGs is unknown.

As for pedHGG driven by germline or somatic DNA replication repair deficiency, including both mismatch repair and/or polymerase-proofreading deficiency, focal irradiation is recommended [98]. TMZ should be avoided in those circumstances, but lomustine can be considered as an adjuvant therapy [99,100]. Moreover, immune checkpoint inhibition is well established to improve survival at progression for these hypermutant gliomas [101] and may be considered a frontline treatment for some patients with favourable genomic and immune biomarkers [102].

5.2. Recurrent/progressive hemispheric high-grade glioma, H3-wildtype and IDH-wildtype patients and diffuse hemispheric glioma H3 G34-mutant

There is currently no standard of care for the treatment of recurrent/progressive hemispheric HGG. All patients should be fully restaged and assessed before considering management options to allow delivery of the most appropriate treatment. The available evidence for the selection of specific treatment strategies for the recurrent/progressive hemispheric HGG is limited and mostly based on retrospective cohort studies on heterogeneously treated patients.

Members of the SIOPE-BTG and the GPOH were surveyed on therapeutic options for recurrent/progressive paediatric and adolescent HGG [103]. Based on the results of this survey, SIOPE HGG Working Group recommends surgical resection, if feasible, at the time of relapse/progression combined with molecular pathology to identify potential targeted therapy, such as BRAF/MEK inhibitor, anti-EGFR therapy, CDK inhibitor. Patients should be enrolled into clinical trials if available.

Given the lack of international cooperative trials for recurrent/progressive hemispheric high-grade glioma, it is reasonable to combine conventional multimodal treatment concepts, including re-irradiation, with targeted therapy based on molecular genetic findings [103,104].

5.3. Diffuse midline glioma H3K27-altered

Currently, there is no available evidence for the selection of specific chemotherapy treatment strategies for DMG *H3K27*-altered. Therefore, the mainstay of treatment is radiotherapy (see Radiotherapy section).

With regard to chemotherapy, the SIOPE HGG Working Group has not managed to reach a consensus on the management of these tumours using the Delphi method [96]. Fifty per cent of the Delphi participants agreed that the recommended treatment regimen is chemoradiation with TMZ, followed, after a TMZ treatment break of approximately 4 weeks, by 6–12 cycles of TMZ, irrespective of *MGMT* promotor methylation status. This management approach is supported by the results of the HIT-HGG-2007 trial (ISRCTN19852453) presented at ISPNO in 2022 [105]. A sub-group analysis showed a 3-month EFS and OS benefit for patients with non-pontine pedHGG treated with TMZ in comparison to a more intensive cisplatinum-based chemotherapy regimen (median EFS 10.7 versus 7.4 months, and 19.3 versus 16.2 months, respectively). This also confirmed other reports supporting TMZ as a better tolerable alternative to other cytostatic therapy [30].

Given that the above results have not been published yet and further subgroup survival analysis is ongoing, the remaining 50 % of the Delphi participants did not support the role of TMZ in the treatment of children with DMG *H3K27*-altered [96]. We hope that future studies might help to resolve this area of controversy.

There is some evidence regarding the efficacy of ONC201, a selective antagonist of dopamine receptor D2/3 (DRD2/3), in H3 K27M-mutant diffuse midline glioma [106]. Data initially presented at ASCO in 2019 showed a response rate of 27 % in supratentorial H3K27M diffuse midline gliomas [107]. This preliminary data still awaits confirmation [108]. The activity appears more convincing for adult and non-brainstem located DMG which is being investigated by currently recruiting BIOMEDE 2.0 trial (NCT05476939). The trial is evaluating efficacy of ONC201 in comparison with everolimus and subsequent to historical controls.

In view of the absence of any meaningful therapy for this lethal disease and some evidence regarding the efficacy of ONC201, a patient may qualify for access to ONC201 following radiotherapy through an expanded access pathway in cases where a clinical trial is not an option [106]. Treating clinicians and patients should note that investigational medicines do not have established safety and efficacy, so all potential risks and benefits should be carefully evaluated before seeking expanded access to unapproved medicines outside of a clinical trial.

If a potential target for therapy is identified following a biopsy, the biological agent should ideally be used within the context of a clinical trial. If enrolment into a clinical trial is not feasible, it is at the discretion of a treating clinician to consider the individual patient, and the risk profile of the drug(s) to ensure the risk-benefit balance is appropriate. Patients and their parents/guardians should be informed of the experimental nature of the treatment and potential side effects. Quality of life aspects should always be taken into consideration for any kind of treatment decisions in these extremely poor prognostic patients.

Therapy should be primarily based on national therapy guidelines, and each plan should be tailored according to the patients' needs.

5.4. Progressive/relapsed diffuse midline glioma H3K27-altered

Similarly, to the *de novo* diagnosis of DMG *H3K27*-altered, currently, there is no evaluated and agreed chemotherapy treatment standard for progressive/relapsed DMG *H3K27*-altered.

If a potential target for therapy is identified following a biopsy and considered at the time of tumour progression/relapse, similar principles apply as in *de novo* diagnosis.

5.4.1. Pontine diffuse midline glioma H3K27-altered (DIPG)

Numerous studies of systemic chemotherapy have failed to demonstrate any significant improvement in survival. Currently, the mainstay of treatment is radiation given with palliative intent (see Radiotherapy section) [109].

A sub-group analysis of the HIT-HGG-2007 trial (ISRCTN19852453), presented at ISPNO in 2022, showed a 2-month EFS benefit for patients with pontine pedHGG treated with TMZ (median 8.2 versus 6.2 months). However, there was no OS benefit for these patients (median OS 11.4 versus 11.3 months) [105].

If a potential target for therapy is identified following a biopsy, the biological agent should ideally be used within the context of a clinical trial. If enrolment into a clinical trial is not feasible, similar principles apply as in the management of other pedHGG.

5.5. Progressive/relapsed pontine diffuse midline glioma H3K27-altered

Similarly, to the *de novo* diagnosis of intrinsic pontine glioma, if a potential target for therapy is identified following a biopsy and considered at the time of tumour progression/relapse, the therapy must be regarded as experimental and ideally would be given in the context of a clinical trial. If the enrolment into a clinical trial is not feasible, similar recommendations apply.

5.6. Infant-type hemispheric HGG

A chemotherapy-only approach has been widely adopted by the paediatric neuro-oncology community worldwide as the preferred treatment option for infants with newly diagnosed HGG. Seventy-five per cent of the Delphi participants agreed that radiation therapy should be avoided in the management of infant-type HGG to prevent significant adverse effects on the developing brain. Indeed, it is now worldwide recognized that radiation is not recommended in young children < 2 years. Poor outcomes and late treatment effects have engendered a reluctance to treat those patients with radiation therapy.

The two currently recommended chemotherapy regimens for treatment of infant-type hemispheric HGG in European countries are the BBSFOP protocol and the modified-HIT-SKK (without intraventricular methotrexate).

The regimens are based on the French chemotherapy-only (BBSFOP) protocol, the German modified-HIT-SKK (without intraventricular methotrexate) chemotherapy-only strategy, and the UK-chemotherapy only approach as per UKCCSG/SIOP CNS 9204 trial:

1. The BBSFOP protocol is a 16-month schedule of 7 cycles of three drug pairs of carboplatin-procarbazine, cisplatin-etoposide, and vincristine-cyclophosphamide [34]. Five-year progression-free survival was 35 % and 5-year overall survival was 59 %, with a median follow-up of 5.2 years. Age range of patients included in the trial was up to 5 years. The drugs selected were a combination of those used with acceptable toxicities in infants and young children with malignant brain tumours [110]. This protocol aimed to develop a mild chemotherapy that could be given for a long period to delay/avoid radiotherapy (Appendix 1).
2. The HIT-SKK chemotherapy (Chemotherapy for Infants and Toddlers with Brain Tumours) is the German strategy to delay and avoid radiotherapy in young brain tumour patients. Patients treated by the HIT-SKK multiagent chemotherapy receive three two-month cycles of chemotherapy consisting of intravenous methotrexate, cyclophosphamide, vincristine, carboplatin, and etoposide [111]. The published outcome data is based on treatment of children diagnosed with medulloblastoma under the age of 4 years [111,112]. The HIT-SKK chemotherapy – in combination with intraventricular methotrexate for young children with medulloblastoma patients – has been shown to be feasible and well tolerated [112]. In infant-type hemispheric HGG, the modified HIT-SKK chemotherapy (without intraventricular methotrexate) is currently frequently used (Appendix 1).
3. In the UK version of this chemotherapy, infants were treated without intraventricular therapy, with courses of carboplatin-vincristine, high-dose methotrexate-vincristine, cyclophosphamide-vincristine and cisplatin monotherapy [35]. Five-year progression-free survival was 18.1 % and 5-year overall survival was 34.7 %. The trial recruited only patients under the age of 3 years. The chosen drugs have different mechanisms of cytotoxic action to prevent the early emergence of drug resistance by alternating courses of myelosuppressive and relatively non-myelosuppressive chemotherapy. The aim was to enhance treatment intensity with chemotherapy given every 2 weeks (Appendix 1).

Given that the European trials were conducted on children of different age (which has an impact on survival outcomes) and before the era of molecular biology, it is at a discretion of the treating clinician to select the preferred treatment regimen according to the institutional settings.

Molecular pathology has recently shed light on molecular groups in infant HGG with distinct survival [40,41]. If possible molecular analysis should be undertaken to detect common gene fusions in ALK, ROS1, NTRK1/2/3 and MET, which may be targetable ideally as part of a clinical trial. Entrectinib, a tyrosine kinase inhibitor known to target NTRK, ALK and ROS1, showed encouriging results in STARTRK-1 trial (NCT02097810) which has led to the subsequent STARTRK-NG (NCT02650401) phase 1/2 trial conducted in children to evaluate entrectinib in solid or primary CNS tumors (NCT02650401). Results in 16 non-infant paediatric patients (median age > 5 years) with primary CNS tumors were promising. Currently recruiting CONNECT1903 study (NCT04655404) is a pilot study evaluating safety and efficacy of larotrectinib in children diagnosed with high-grade glioma with NTRK fusion. Infantile gliomas are mostly single-driver tumours and, therefore, they should be suitable for treatment with targeted therapy [36]. The promising preliminary data still awaits confirmation. Market authorization of entrectinib and larotrectinib also still limit their application to children with NTRK fusion gene-positive tumours in the absence of adequate other treatment options which are present for infant HGG. For ALK and ROS1 positive paediatric tumours there is still no market authorization for entrectinib. Therefore, precision medicine approaches are currently not recommended in childern with a new diagnosis of infant-type hemispheric HGG.

6. Conclusion

The levels of evidence for treatment recommendations for children diagnosed with pedHGGs are limited. Numerous efforts to generate new evidence by doing prospective studies pointing at this unmet need in neuro-oncology are ongoing. Translating and adapting adult treatment recommendations into paediatric practice can be challenging and might inadvertently lead to inappropriate management. Therefore, the medical community needs to develop research studies for this rare disease group, including investigation into the biology of diseases and treatment options.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2024.100210.

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