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# Medulloblastoma therapy: Consensus treatment recommendations from SIOP-Europe and the European Research Network

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ABSTRACT

The treatment of medulloblastoma has evolved considerably over the last 10 years. Treatment intensity is now stratified within clinical trials, using risk-associated clinical features and molecular biomarkers, aimed at maximising cure rates whilst minimising long-term disease and therapy-associated side-effects. In Europe, we have developed a long-term strategy of using randomised trials to test stratified treatments across all medulloblastoma disease demographics, and to investigate further stratification using biological analysis of the samples collected. Importantly, care must be taken not to adopt experimental arms from trial protocols into routine practice, prior to trials' results being available. Moreover, there are time periods when trials are not open to recruitment for all the various risk-groups. These guidelines, developed under the auspices of SIOP-Europe and the European Research Network, review recent and current trials, alongside the literature, to provide evidence-based guidance for the contemporary therapy of medulloblastoma.

## 1. Background

Medulloblastoma is the most common malignant brain tumour in children and young people, with approximately 650 new cases per year in the European Union (EU). These small, round, blue cell tumours of the posterior fossa account for 15–20 % of all brain tumours in children. The median age of diagnosis is 7 years, but medulloblastoma occurs at all ages and into adulthood. Medulloblastoma is now regarded to represent

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a basket term for different disease types with different cells of origin, biology, genetics and clinical behaviour. The following medulloblastoma types are defined in the 2021 World Health Organisation (WHO) classification of central nervous system (CNS) tumours [1,2]:

1) Medulloblastoma, molecularly defined, comprising:

a. Medulloblastoma, WNT-activated
b. Medulloblastoma, SHH-activated and *TP53*-mutant
c. Medulloblastoma, SHH-activated and *TP53*-wildtype
d. Medulloblastoma, non-WNT/non-SHH

2) Medulloblastoma, histologically defined, comprising;

a. Classic Medulloblastoma
b. Desmoplastic / nodular Medulloblastoma,
c. Medulloblastoma with extensive nodularity
d. Large-cell / anaplastic medulloblastoma

Currently, treatment decisions are based upon biological and pathological medullloblastoma types, molecular biomarkers, staging, age at diagnosis and possible genetic predisposition.

Our understanding of these medulloblastoma types, and their clinical relevance, is evolving and altering our understanding of prognosis and risk, together informing a shifting scope of best-practice for disease stratification [1,3,2]. Initially, stratification was based on clinical factors associated with a poorer prognosis (i.e. metastatic disease, histology and the presence or absence of residual disease post initial surgery). Subsequently, advances in molecular typing have refined this initial stratification. Although risk stratification is in constant evolution, Tables 1 and 2 outline the best practice based on current evidence.

**Table 1**
Risk groups for children aged 3–5 years old and over.

| | Molecular features | Histology | Residual disease | Metastatic disease |
|---|---|---|---|---|
| **Low-risk** | WNT subgroup (under 16 years old) *TP53* wildtype *MYC/N* non-amplified | Classic, Desmoplastic / nodular | $< 1.5\ cm^2$ | M0 |
| **Standard-risk** | *TP53* wildtype *MYC/N* non-amplified (except Group 4 *MYCN* amplified) | Classic, Desmoplastic / nodular | Any | M0 |
| | WNT subgroup (any age and not low-risk) | Classic, Desmoplastic / nodular | Any | M+ if under 16<br>M0 if over 16 |
| | non-WNT subgroup No biological high-risk features | Classic, Desmoplastic / nodular | $\geq 1.5\ cm^2$ | M0 |
| **High-risk** | *TP53* mutant and / or *MYCN* amplified (except Group 4 *MYCN* amplified) | Any | Any | Any |
| | Any non-WNT and WNT > 16 years | Any | Any | M+ |
| | *MYC* amplified | Any | Any | Any |
| | Any | Large-cell / anaplastic | Any | Any |

**Table 2**
Risk groups for children aged < 3–5 years.

| | Molecular features | Histology | Residual disease | Metastatic disease |
|---|---|---|---|---|
| **Low-risk** | SHH-*TP53* wildtype *MYC/N* non-amplified | DN/MBEN | Any | M0 |
| **Standard-risk** | not high-risk non-WNT | Classic | Any | M0 |
| | SHH-*TP53* wild-type *MYC/N* non-amplified | DN/MBEN | Any | M+ |
| **High-risk** | *TP53* mutant and/or *MYC/N* amplified | Any | Any | Any |
| | non-SHH, non-WNT | Classic | Any | M+ |
| | Any | Large-cell / anaplastic | Any | Any |

### 1.1. Molecular disease groups

The discovery of molecularly-defined disease groups within medulloblastoma represents the most fundamental advance. International consensus, reached in 2012, recognised four principal molecular disease groups – WNT, SHH, Group 3 and Group 4 [4]. Each group is defined empirically by its characteristic genome-wide transcriptomic and DNA methylation patterns [4–6] and displays characteristic clinico-pathological features. WNT and SHH are synonymous with their WHO clinical types (above); WNT (wnt/wingless pathway) and SHH (sonic hedgehog pathway) activated medulloblastomas are caused by mutations in their respective developmental signaling pathways [1,2,7]. SHH activated medulloblastomas were subsequently placed into two clinical types within the WHO classification, defined by the presence or absence of *TP53* mutations, that have to be separated [6,8]. Group 3 and Group 4 medulloblastomas represent overlapping disease groups [1,2], and together comprise the WHO-defined 'non-WNT/non-SHH medulloblastoma' disease type.

Childhood WNT patients (<16 years at diagnosis) consistently show a favourable prognosis (>90 % survival) [9-13]. Clinically significant biological heterogeneity is evident within each non-WNT group; for instance, *TP53* mutations associate with a poor outcome in SHH [6,8] and non-WNT/non-SHH medulloblastomas harbour few mutations but multiple DNA copy number alterations [14-16]. Importantly, both histological and molecular typing, including *TP53* status, have been integral to the WHO medulloblastoma classification since 2016 and are considered 'standard-of-care' [1].

More recently, 8 further consensus subgroups (termed 1-8) have been defined within non-WNT/non-SHH (Groups 3 and 4) medulloblastomas [2,6,15,17,18], and four subgroups (1-4) within SHH disease [6,17,19,20], again characterised by unique (epi)genomic signatures, clinical and pathological features. *TP53* mutations predominantly occur in SHH subgroup 3, associated with non-infant disease [2,6,17,20]. These subgroups are reflected in the WHO 2021 classification [1,2], but their relevance and role in clinical practice remains to be defined.

### 1.2. Prognostic biomarkers

In addition to WNT and SHH/*TP53*-mutant tumours, the presence of *MYC* or *MYCN* amplification (unless Group 4 with *MYCN* amplification) have been consistently identified as independent prognostic factors in trial and non-trials based studies [6,13,14,21–23]. *MYC/MYCN* amplification is also commonly associated with metastasis and large cell/anaplastic (LCA) histology [6,21,22]. Schema which incorporate these combined factors significantly outperform risk-stratification using clinical factors alone [6,21].

The prognostic significance of *MYC/MYCN* amplification and histology is likely to be relevant only in the context of molecular group/type (e.g. *MYC* amplification in Group 3 non-WNT/non-SHH medulloblastomas; *MYCN* amplification in SHH only) [6,13,14,16,23,24]. *MYCN* amplification was considered a disease-wide high-risk factor in the original SIOP-PNET5-MB protocol, based on its association with a poor prognosis in studies undertaken across the disease prior to identification of the four principal molecular groups [13,21,22]. Two large retrospective studies have since assessed the prognostic impact of *MYCN* amplification with reference to disease types/groups [6,23]. In both, *MYCN* amplification was associated with both SHH and non-WNT/non-SHH medulloblastoma Group 4, but displayed different relationships to clinical outcome in each. In SHH, *MYCN* amplification was associated with a poor prognosis and commonly co-occurred with other high-risk factors (LCA pathology, TP53 mutation, M+ disease). In contrast, *MYCN* amplification in Group 4 was not associated with a worse prognosis. These associations have subsequently been validated in four further cohorts, including the HIT-SIOP-PNET4 clinical trial [13,14,24,26].

Importantly, emerging biological risk factors have clear potential to further understand disease heterogeneity and improve the stratification of risk. These now require urgent evaluation and/or validation in the clinical trials setting. In the non-infant disease, these include favourable-risk molecular subgroups (subgroups 6 and 7) within non-WNT/non-SHH medulloblastomas [2,6,13–15,18,26], poor-risk metastatic disease in Group 4 tumours [3,6,14], and favourable-risk whole--chromosome aberration (WCA) phenotypes in non-WNT/non-SHH tumours [13,14,26]. Initial studies have demonstrated these factors can be used together to differentiate favourable-risk (FR; >90 % 5-year survival), standard-risk (SR; >75 % 5-year survival), high-risk (HR) and very high-risk (VHR; <40 % 5-year survival) disease groups within non-infant medulloblastoma, and will be used as a basis for novel stratification schemes in the upcoming SIOP-MB-6 clinical trial [13,14,26].

Young children with medulloblastoma (age less than 5 years) are responsible for approximately 40 % of cases of medulloblastoma that occur in children, these can be split by biological markers into a low-risk group defined by SHH-activation and a high-risk group defined by non-WNT/non-SHH biology [19]. The prognostic significance of the SHH-1 and SHH-2 subgroups, which dominate in young children with SHH disease, is uncertain. While prognostic in some studies [27,28], with either HeadStart [29] or HIT SKK treatment with intraventricular methotrexate [30], this subgrouping does not seem to play a major prognostic role. Young children with SHH medulloblastoma have a high-risk for Gorlin syndrome, *PTCH1*, *SUFU* or *ELP1* germline mutations [20], with important implications for radiotherapy, emphasizing the need not to jeopardize radiotherapy-free survival in these especially vulnerable patients.

Young children with non-SHH activated medulloblastoma (excluding WNT activated medulloblastoma which is extremely rare in this age group) are considered high or very high-risk depending on the presence of other risk factors such as *MYC* amplification and large-cell / anaplastic histology [19]. Intensive treatment including high dose therapy is considered as standard in treating this group of young people.

### 1.3. Constitutional genetic predisposition

Familial disease/germline mutations describe a notable proportion of medulloblastomas (5–10 %); predominantly associated with Gorlin syndrome (*PTCH1/SUFU* mutation in SHH-*TP53* wildtype patients), Turcot syndrome (*APC* mutations in WNT patients), Li-Fraumeni syndrome (a subset of SHH-*TP53* mutant patients), Fanconi's Anaemia (*BRCA2/PALB2*, subgroup unknown) and *ELP1* (in SHH patients) [20]. These have been associated with systemic radio- and chemo-sensitivity and must also be considered in therapy selection.

The patient group with SHH-activated medulloblastoma and *TP53* mutation is a notable minority group with an annual accrual of approximately 5–10 patients in Europe. This group is commonly associated with the SHH-3 subgroup, LCA histology and *MYCN* amplification, has a very poor prognosis. Those with somatic *TP53* mutations are treated on conventional high-risk protocols, however there is currently no consensus on the treatment of SHH patients with germline *TP53* mutations (Li-Fraumeni syndrome), which represent the majority (57 %) [6,20]. The loss of p53 function is thought to confer resistance to chemotherapy, [26,31] and effective anti-tumoural treatments have yet to be established. Moreover, chemotherapy-related toxicity and secondary malignancies are of great concern in patients with germline *TP53* mutations [32]. Alkylating drugs especially seem to exert a high genotoxic stress in *TP53*-deficient backgrounds [27]. In a historic cohort of 37 patients with SHH-activated, germline *TP53*-mutated medulloblastoma treated with surgery, chemotherapy and radiotherapy, 3 and 5-year EFS were 20 % and 16 %, respectively, with no long-term survivors reported [33]. No difference in OS and PFS was detected when patients were treated with chemotherapy before RT, as compared to RT immediately after surgery, suggesting that chemotherapy before radiotherapy (i.e. a delay of radiotherapy) does not significantly influence outcome (both PFS and OS). Optimal treatment for patients with *TP53* germline mutations (Li-Fraumeni syndrome) is not yet clear although many still treat these children with conventional chemotherapy due to a small proportion having a 5 year EFS)

In summary, medulloblastoma is an 'umbrella' term encompassing multiple WHO-defined disease types alongside the presence of further heterogeneity at the molecular, clinical and outcome levels. The stratified use of risk-adapted therapies should be considered based on best available evidence.

### 1.4. Medulloblastoma in children

Standard-of-care treatment for this group of patients typically comprises maximal safe surgical resection, followed by craniospinal irradiation (CSI) and chemotherapy (CT), with therapy intensity adapted according to disease risk. This combination leads to long-term survival rates of 60–80 %. For children less than 5 years of age a radiotherapy sparing approach is advocated where possible.

### 1.5. Favourable-risk disease

Children with WNT medulloblastoma have the most favourable outcomes of all disease groups. Several studies globally, both prospective and retrospective, have shown that WNT patients under the age of 16, and without evidence of other high-risk features, have an excellent survival independent of the protocol they have been treated with, including the prospective PNET3 (The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET3 Study)[11,21,34], HIT-SIOP PNET4 [9,13,35] and SJMB96 (St Jude Medulloblastoma 96) [12] studies, which showed that non-metastatic WNT patients treated with surgery, CSI+ /− chemotherapy have survival rates > 95 % 5-year PFS). Patients over the age of 16 with WNT tumours are not considered favourable-risk [3] as has been confirmed in a number of retrospective studies [9,13,36,37].

The omission of craniospinal radiotherapy for this group of children has been examined in 2 small studies, the first using a chemotherapy only approach which was terminated after the first 2 children relapsed [38] and another in which chemotherapy plus focal radiotherapy was used, which also demonstrated a significant rate of relapse in the neuroaxis [39]. It appears that currently craniospinal radiotherapy is necessary for a favourable outcome.

Subsequently, the newest generation of biologically-informed clinical trials, specifically PNET5 MB, SJMB12 (St Jude Medulloblastoma 12) and COG (Childrens Oncology Group) ACNS 1422, are evaluating de-escalation of radiotherapy dose whilst maintaining survival for patients with WNT tumours, in order to reduce therapy-related morbidity

[3,40] (Table 3).

### 1.6. Standard-risk disease

In multiple studies from the last 2 decades, 5-year EFS and OS rates of > 70 % have been reported in children with non-disseminated disease at time of diagnosis. Potential reasons underpinning these rates include the routine employment of more extensive surgery aimed at maximal safe resection; more refined preoperative evaluations (i.e. radiology), resulting in a clearly defined group of children with non-disseminated disease; and the use of adjuvant CT during and after RT [42], as well as improved radiotherapy techniques and equipment.

Over time, the 'standard-risk' concept has become more detailed and precise. Current imaging, pathology and molecular diagnostic practice now allows better definition and stratification of the standard-risk group. The currently accepted definition of standard-risk includes (i) no evidence of disseminated disease on MRI of the entire brain and spine performed pre- or postoperatively as well as on cytological examination of lumbar CSF performed between 14 days of surgery and the onset of radiation, (ii) histology should be either classic, desmoplastic/nodular or medulloblastoma with extensive nodularity, (iii) tumours should have no evidence of *MYC* amplification, *MYCN* amplification (except Group 4) and should not be SHH-*TP53* mutant. Historically, patients needed to have < 1.5 $cm^2$ of residual tumour (based on maximum dimensions on an axial view) on postoperative MR imaging performed within 72 h of surgery, although this risk feature has been recently reconsidered (see section on residual disease below).

Considering the evolution of the 'standard-risk' definition, comparisons between study cohorts can be difficult [42]. Nonetheless, the 5-year overall survival (OS) for standard-risk medulloblastoma patients included in recent clinical trials is reported to be around 80 % (Table 4).

**Table 3**
Trials including Low-Risk Medulloblastoma (adapted from Thompson et al. [40]).

| Study | ClinicalTrial.gov Number | Phase | Treatment | Key features |
|---|---|---|---|---|
| **PNET 5 MB** [25] | NCT02066220 | II/III | Risk-specific radio- and chemotherapy | Low-risk: Reduced-dose craniospinal irradiation (18 Gy) + Boost to tumor bed (total 54 Gy), Maintenance chemotherapy consisting of 3 courses of cisplatin, CCNU, and vincristine alternating with 3 courses of cyclophosphamide and vincristine |
| **SJMB12** [41] | NCT01878617 | II | Risk-specific radio- and chemotherapy | Reduced-dose craniospinal irradiation (15 Gy), Lower dose of cyclophosphamide |
| **COG ACNS1422** | NCT02724579 | II | Reduced craniospinal radiotherapy | Reduced craniospinal radiotherapy (18 Gy) with a limited target volume boost to the tumor bed of 36 Gy for a total of 54 Gy Reduced chemotherapy (no vincristine during chemotherapy and reduced-dose maintenance chemotherapy) |

At present, the emerging trials' philosophy is to investigate strategies to de-escalate therapy, considering the acute and late-effects. Proton beam therapy is becoming increasingly used for patients with medulloblastoma, aimed at reducing treatment-related sequelae. The results from a 2016 case-matched analysis of patients with standard-risk medulloblastoma treated with proton and photon RT demonstrated no difference in patterns of failure, recurrence-free survival, or overall survival according to RT modality. Thus, disease control with protons and photons appears to be equivalent [44]. There appears to be a reduction in long term late effects using proton beam radiotherapy although long term studies are not yet available [45]. It should be noted that de-escalation of therapy across the board without biological evidence is discouraged after the results of the ACNS 0331 study (reduced radiation in younger patients under 8 years with M0R0 disease) showed this not be safe [46].

Presently there are two major trials in standard-risk medulloblastoma, which are awaiting reporting of results:

SIOP-PNET5-MB: Favourable-risk patients (WNT subgroup tumours with no other risk-factors) were treated with 18 Gy CSI, 54 Gy boost to the tumour bed **a**nd 6 cycles of maintenance chemotherapy (3 courses of cisplatin, CCNU and vincristine alternating with 3 courses of cyclophosphamide and vincristine). Standard-risk patient were randomized in one of 2 arms: the aim was to test whether concurrent carboplatin (35 mg/$m^2$ 5 times/week) during radiotherapy (23.4/54 Gy) with both experimental and control groups receiving after RT 8 cycles of maintenance chemotherapy (4 courses of cisplatin, CCNU and vincristine alternating with 4 courses of cyclophosphamide and vincristine) [25].

SJMB12: Here, the standard-risk group was divided in 3 strata determined by analysis of the tumour tissue for tumour biomarkers: WNT (Stratum W1 – reduction of radiotherapy dose to 15 Gy CSI + boost to 51 Gy), SHH (Stratum S1 – positive for SHH biomarkers) and non-WNT/Non-SHH / failed / indeterminable (Stratum N1 – negative for WNT and SHH biomarkers or results are indeterminable). All except clearly defined WNT tumours received standard dose CSI with boost to the primary tumour site (23.4/54 Gy), followed by 4 cycles of maintenance chemotherapy (cisplatin, vincristine, cyclophosphamide). In stratum S1, after completion of 4 cycles of chemotherapy, participants who were skeletally mature received maintenance chemotherapy with vismodegib (NCT01878617).

### 1.7. High-risk disease

Prior to the 1990s, the outcome for patients with high-risk disease was poor, with 5-year EFS < 50 % [34,47–50]. To improve survival, regimens looked to intensify treatment, either by increasing the dose of radiation, using high- dose chemotherapy and stem cell rescue, intensive chemotherapy regimens or radiosensitisers. Since then, there have been several modestly-sized or institutional studies that have achieved 5-year EFS rates of around 60 % (summarised in Table 5) [12,51–55]. The approaches used in these were based on national or institutional treatment experience and included (i) high-dose chemotherapy prior to (or occasionally post-) craniospinal RT [12,43,52] (ii) HART (Hyperfractionated and Accelerated Radiotherapy); twice daily for 23 days [23,52,55] and (iii) conventional craniospinal RT (once daily), most commonly prior to maintenance chemotherapy [53,54]. A recent paper has suggested that the addition of carboplatin as a radiosensitiser in Group 3 patients offers a survival advantage [56] although the numbers were relatively small and follow-up limited, these findings have not yet been independently validated.

Patient cohorts in these studies, however, are typically small and often selective. In addition, the criteria for risk stratification have varied over time and between studies. None considered biological stratification or disease group analysis. High-risk medulloblastoma in the non-infant group is now considered to include those with non-WNT tumours and positivity for one for the following factors; (i) the presence of metastatic disease, (ii) the presence of LC/A histology, (iii) the presence of *MYC*/

**Table 4**
Standard-risk medulloblastoma trials.

| Study | Number | Radiotherapy dose | Definition of Standard-risk | Chemotherapy | Comments | Toxic Deaths | Progression on treatment | Event free survival (EFS) |
|---|---|---|---|---|---|---|---|---|
| **SFOP** [43] | 136 | 55 Gy to the PF and 25 Gy to the brain and spine (fraction of 1.8 Gy, 5 days per week) | Total or subtotal tumour resection, no visible metastases on craniospinal magnetic resonance imaging (MRI), and no meningeal dissemination on postoperative lumbar puncture CSF cytology | Two courses of eight drugs (vincristine, carmustine, methylprednisolone, procarbazine, cisplatine, cyclophosphamide, cytarabine, hydroxyurea) administered in 1 day in followed by two courses of etoposide plus carboplatin (500 and 800 mg/m2 per course, respectively) were administered after surgery, pre-irradiation | National prospective study. No randomization. | 0 | 47<br>4 PF only<br>23 PF + Brain or spine 20<br>Brain or spine only | 5-year EFS 64.8 %<br>But 4 % of patients were wrongly included: after review,<br>5-year EFS 71.8 % |
| **A 9961** [42] | 379<br>A: 193<br>B: 186 | 23,40 Gy CSI + PF boost 32,4 Gy (total dose 55,8 Gy), fractions of 1,8 Gy/ day, 5 days/week | Residuum < or = 1.5 cm2 and M0 disease | Randomization after surgery – CT 8 cycles: Regimen A: CCNU, cisplatin, and vincristine<br>Regimen B: cisplatin, cyclophosphamide, and vincristine<br>During radiotherapy, both regimens were treated with weekly vincristine | Multi-institutional study<br>Randomized | 0 | 73 (63 assessable patients)<br>32 % PF only<br>40 % Brain /Spine only<br>25 % PF+ Brain /Spine | 5-year EFS 81 %<br>A: 82 %<br>B: 80 % |
| **SJMB96** [12] | 86 | 23.4 Gy | Residuum < or = 1.5 cm2 and M0 disease | 4 x HD chemotherapy post radiation (cisplatin, cyclophosphamide and vincristine) | Single institute study. No randomization. | 0 | 3 PF only<br>1 PF + Brain or spine 9<br>Brain or spine alone | 5-year EFS 83 % |
| **HIT/ SIOP PNET 4** [35] | 338<br>STRT: 169<br>HFRT: 169 | STRT:<br>23.4 Gy to the CS axis and 54 Gy to WPF (42 days, 30 fractions of 1.8 Gy, 5 days per week)<br>HFRT:<br>36 Gy to the CS axis and 60 Gy to WPF with a further boost to a total of 68 Gy to the tumor bed, (48 days, 68 fractions of 1.0 Gy 2x/ day) | Residuum < or = 1.5 cm2 and M0 disease | Both treatment arms:<br>Vincristine during RT (maximum of 8 doses) plus 8 cycles of adjuvant chemotherapy (cisplatin, lomustine and vincristine) | Multi-institutional study<br>Randomized. | 1 | 0 | 5-year EFS 79 %<br>STRT: 78 %<br>HFRT: 81 %<br>EFS of children with all reference assessments and no large residual tumor was 82 % ± 2 % at 5 years. |

*MYCN* amplification (not including Group 4 *MYCN* amplified tumours with no other risk factors) and (iv) SHH-*TP53* mutant tumours. As discussed below, the presence of residual disease > 1.5 $cm^2$ without other risks factors is not considered to constitute high-risk disease.

The relative merits of these alternative treatment approaches for high-risk disease have not been tested in a systematic way, with respect to the heterogeneous disease biology we now appreciate, or in a large randomised multi-national trial, to ascertain whether any of these strategies offers a survival advantage. In addition, their relative associated toxicities or late-effects have not been assessed. Currently SIOPE has a large multi-national randomised trial open (SIOP-HRMB) [25] which is comparing 3 treatment strategies following induction with carboplatin and etoposide, namely standard CSI radiotherapy (protons or photons) vs hyperfractionated and accelerated radiotherapy (HART) vs tandem thigh dose thiotepa with stem cell support followed by standard CSI radiotherapy [25].

A number of studies have shown that the presence of residual disease with no other clinical or biological risk factors behaves as standard-risk disease and should be treated as such. This is irrespective of treatment received [59–61].

### 1.8. Medulloblastoma in infants and young children (iMB)

Treatment of medulloblastoma in infants and young children (defined as age less than 3–5 years at diagnosis, depending on country; hereafter referred to as infant medulloblastoma (iMB) employs a different treatment philosophy to older children and young people; iMB treatment is typically focused on surgical resection followed by chemotherapeutic approaches, with the aim of avoiding or delaying the use of CSI, due to the highly deleterious acute and late-effects associated with delivery of radiotherapy to the very young. Studies to date have included conventional systemic chemotherapy alone (e.g. UKCCSG) or in combination with focal radiotherapy (COGP9934, SJYC07) or intrathecal chemotherapy (HIT-SKK92), or high-dose chemotherapy with autologous stem cell rescue (HeadStart). SHH and non-WNT/non-SHH Group 3 disease (both approximately 40 % of iMB cases) predominate in this age group [19,28,62].

### 1.9. Sonic hedgehog (SHH) and desmoplastic-nodular iMB disease

The majority of iMB-SHH belong to the SHH-*TP53*-wildtype molecularly defined type. The related desmoplastic/nodular (DN) and medulloblastoma with extensive nodularity (MBEN) histology variants are almost exclusively found in this disease type in this age group, with the MBEN variant more common in younger iMB-SHH cases. A notable proportion of iMB-SHH-*TP53*-wildtype tumours (~20 %) display classic, and rarely LCA, histology [19]. Results of retrospective and prospective studies demonstrated that infants with SHH-driven medulloblastoma show a more favourable clinical outcome than those with non-WNT/non-SHH disease [4,19].

**Table 5**
Summary of clinical studies undertaken in high-risk medulloblastoma. None of these studies were biologically stratified, so interpretation of the results in the molecular era is difficult. SJMB – St Jude Medulloblastoma Study, HART – Hyperfractionated Accelerated Radiotherapy, HFRT – Hyperfractionated Radiotherapy, COG – Children's' Oncology Group, POG – Pediatric Oncology Group, STR – subtotal resection, HDCT – high dose chemotherapy. M = metastatic status; M0 = no evidence of metastatic disease, M1 = positive CSF cytology, M2 = metastasis within the cranial vault, M3 = MRI visible spinal metastatic disease, M4 = metastasis outside the CNS.

| Study | Number of Patients | Radiotherapy dose | Definition of High-risk | Chemotherapy | Comments | Toxic Deaths | Progression on treatment | Event free survival (EFS) |
|---|---|---|---|---|---|---|---|---|
| **SJMB96** [12] | 48:<br>M0 = 6;<br>M1 = 9;<br>M2 = 6;<br>M3 = 27 | 36 – 39.6 Gy | Residuum > 1.5 $cm^2$ or M1-M3 disease | 4 x HD chemotherapy (cisplatin, cyclophosphamide and vincristine) post radiation | Single institute study. No randomisation. Part of a larger trial. 31/48 additional pre- radiation topotecan window study<br>Quality of survival data published | 0 | 1 | 5-year EFS 70 % |
| **HART (UK)** [57] | 34:<br>M1 = 9;<br>M2 = 3;<br>M3 = 24 | 1.24 Gy fractions bd to 39.68 Gy | Only M+ patients | Vincristine with radiation<br>Maintenance 8 x cisplatin, CCNU, vincristine | Toxic feasibility study and not powered for survival. Excluded patients requiring GA. | 1 | 0 | 3-year EFS 59 % |
| **COG 99701** [53] | 161<br>Centrally reviewed:<br>M0 = 5;<br>M1 = 18;<br>M2 = 10;<br>M3 = 49 | 36 Gy | Residuum > 1.5 $cm^2$, M+ and supratentorial PNET (all stages) | Carboplatin and vincristine during radiation<br>Maintenance with 6 x cyclophosphamide and vincristine + /- cisplatin | Phase I/II carboplatin as radiosensitiser. No quality of survival data published. | 0 | 4 (all long- term survivors, likely pseudo progression) | 5-year EFS<br>M1 = 77 %<br>M2 = 50 %<br>M3 = 67 % |
| **POG 9031** [54] | 224:<br>M1 = 29;<br>M2 = 36;<br>M3 = 34;<br>M4 = 9 | 35.2 – 40.0 Gy | T3b/T4 at the time of surgery (72), M+ (108) or residuum > 1.5 cm3 (44). | Randomised 3 x cisplatin and etoposide before or after radiation<br>Maintenance with 7 x cyclophosphamide and vincristine | 72 were Chang Stage T3b/T4, M0, no residual.<br>No quality of survival data published | None reported | 12 in the CT 1st arm | 5-year EFS<br>66 % CT $_1$st<br>70 % RT 1st |
| **Milan** [52] | 33:<br>M1 = 9;<br>M2 = 6;<br>M3 = 17;<br>M4 = 1 | HART 31.2 – 39 Gy | Only M+ patients | 10 weeks chemotherapy pre-radiation (methotrexate, vincristine, etoposide, cyclophosphamide, carboplatin)<br>Post radiation 2 x HD chemotherapy (Thiotepa) or maintenance with 12 moths CCNU and vincristine | Limited centre study<br>Subsequent neuro toxicity reported. | None reported | 5 (pre-radiation)<br>2 (on maintenance therapy | 5-year EFS 70 % |
| **Institut Gustave Roussy (France)** [51] | 24:<br>M0 = 5;<br>M1 = 0;<br>M2 = 4;<br>M3 = 15 | 18 Gy (1)<br>25 Gy (2)<br>36 Gy (19)<br>40 Gy (1)<br>54 Gy focal (1 sPNET) | Residuum > 1.5 $cm^2$, M+ disease, *MYCN* amplification or supratentorial PNET (3) | 2 x carboplatin and etoposide pre- radiation<br>2 x HD chemotherapy (Thiotepa) Maintenance with temozolamide | Single institute study<br>Neurocognitive data reported | 0 | 0 | 5-year EFS 65 %<br>5-year EFS 72 % in metastatic MB |
| **HIT 2000 (Germany)** [30] | 123<br>M1 = 36<br>M2 /<br>M3 = 87 | HFRT 40 Gy | Only M+ patients | 2 x cycles of pre-radiation chemotherapy (cyclophosphamide, vincristine, methotrexate, carboplatin, etoposide and intraventricular methotrexate)<br>Maintenance with 4 cycles cisplatin, CCNU, vincristine | Well tolerated. | 0 | 14 (pre-radiation)<br>1 (after radiation)<br>31 (during maintenance or at end of treatment) | 5-year EFS 62 % |
| **PNET HR + 5 France** [58] | 51<br>M0 = 14<br>M1 = 3<br>M2/3 = 34 | 36 Gy CSI<br>Unless Residual disease alone then 23.4 Gy | Residuum > 1.5 $cm^2$, M+ disease, *MYCN/MYC* amplification, LCA histology | Carboplatin/etoposide x 2<br>Thiotepa HD x 2<br>Temozolomide Maintenance x 6 | French National Study | | | 5 year EFS 76 %<br>5 year OS 76 % |

iMB-SHH tumors are mainly distributed across the SHH-1 and SHH-2 subtypes, with somewhat different copy-number profiles and outcomes in some studies [19,20,28,30]. In initial studies, SHH-1 tumors were found more frequently metastatic and had a worse overall survival compared with SHH-2. SHH-2 are enriched for MBEN histology, and associated with better outcomes. However, first data suggest that prognostic differences between SHH-1 and SHH-2 may be treatment-dependent, however this issue requires clarification in larger, definitive clinical trials [19,27,28,30,31].

The SHH-related DN and MBEN iMB types have formed the basis of cohort selection in the majority of iMB clinical trials conducted to date. The DN/MBEN types are associated with improved survival; in this group of young patients, radiation therapy may be successfully omitted [27,29]. Radiation-sparing treatments examined typically involve

systemic chemotherapy with intraventricular therapy (HIT-SKK'92 protocol) or high-dose chemotherapy with stem cell rescue [27,33,63] (CCG-99703 protocol) [64]. The best reported 5-year PFS is 93 % for patients with non-metastatic DN/MBEN in the German HIT 2000 trial, which combined intraventricular and high-dose intravenous methotrexate with conventional chemotherapy [30] In the CCG-99703 trial, 5-year PFS was 78.6 % for patients with DN/MBEN who received conventional chemotherapy followed by repeated cycles of myeloablative chemotherapy.

Notably, the ACNS1221 and SJYC07 studies omitted intraventricular MTX or high-dose chemotherapy with autologous stem cell support, and performed post-hoc molecular profiling. These revealed inferior outcomes across all SHH medulloblastoma, including both SHH-1 and SHH-2. More specifically, for the SHH-2 subgroup, both ACNS1221 and SJYC07 reported PFS below 70 % (ACNS 1221 – 66.7 % and SJYC07 - 74.5 %), suggesting that even for this seemingly good performing subgroup, intensification of therapy is required [27,28]. The propensity for local relapses, particularly for SHH-2, in both ACNS1221 and SJYC07 suggest that additional measures for local control are required.

The incorporation of either autologous transplant, such as in the HeadStart studies and CCG99703, or the use of intraventricular MTX alongside systemic conventional chemotherapy, is thus considered as the current 'gold-standard' therapy or 'standard of care' for iMB-SHH with DN/MBEN histology [29,33] (Table 6). The treatment of iMB-SHH with metastatic disease is less clear although most groups now opt for high-dose based therapy. Outcomes for iMB-SHH with non-desmoplastic / non-MBEN histology are less clear, and require investigation in prospective studies.

### 1.10. Standard and high-risk iMB

In contrast to the favourable prognosis of DN/MBEN iMB belonging to the SHH-*TP53* wildtype molecular type, the outcome of iMB with classic or LCA histology (predominantly non-WNT/non-SHH Group 3) remains poor [62,63] (Table 7).

Conventional chemotherapy has been used in several clinical trials in this group. With the aim of reducing poor neuropsychological outcome of children after chemotherapy and craniospinal irradiation, intraventricular methotrexate was introduced as a substitute for radiotherapy in the HIT-SKK'92 trial. In this study, twenty-three patients with classic histology had significant worse 5-year PFS and OS rates (34 +/-10 % and 41 +/-11 %), than twenty patients with DN disease (85 +/-8 % and 95 +/-5 %), independent of presence or absence of metastasis or post-operative residual tumour [65]. The UKCCSG 9204 study reported 31 medulloblastoma patients treated with chemotherapy blocks of alternating myelosuppressive and non-myelosuppressive drugs at 14-day intervals for one year or until progression. Of these, 6 were classic and 5 LCA variants; with a 5-year OS of 33.3 % and 0.0 % respectively [66]. In the HIT2000 trial, 19 patients with DMB/MBEN had better EFS and OS rates (5-year rates, 95 % +/-5 % and 100 % +/-0 %, respectively) than 23 patients with CMB (5-year rates, 30 % +/-11 % and 68 % +/-10 %, respectively). Following this confirmation of the poor survival rates and frequent local relapses of patients with non-DN/MBEN disease, local radiotherapy was recommended for all children aged > 18 months with CMB or LC/A MB, but did not translate into improved outcome rates [69].

In the Children's Oncology Group study P9934, 72 young children with non-metastatic medulloblastoma were evaluated. They received four cycles of induction chemotherapy, followed by age- and response-adjusted focal radiotherapy to the posterior fossa (18 or 23.4 Gy) and tumour bed (50.4 or 54 Gy). The 4-year EFS and OS for patients with DN tumours were 58 % (+/-8 %) and 79 % (+/-7 %), respectively, and 23 % (+/-12 %) and 31 % (+/-16 %) for patients with non-DN/MBEN disease. Among 29 patients with documented disease progression, primary site failure was observed in 7/10 patients who progressed before radiotherapy. In contrast, failure outside the posterior fossa occurred in 15/19 patients who progressed after radiotherapy [68]. Thirty-four non-SHH patients were treated in the SJYC07 trial, with risk-adapted treatment with induction chemotherapy, consolidation with focal radiation (intermediate-risk) or chemotherapy (high-risk), and metronomic maintenance therapy. The 5-year EFS and OS were 10.6 % and 50.5 % respectively [28].

The HeadStart I and II studies, consisted of five cycles of induction chemotherapy followed by consolidation phase with one cycle of myeloablative chemotherapy with autologous stem cell rescue. The 5-year EFS and OS were 42 % and 67 %, respectively [62]. Compared to the Head Start I trial, the CCG-99703 study used a shorter number of induction cycles (three versus five) followed by three 'mini' marrow ablative courses of chemotherapy instead of one single more intensive marrow-ablative course, which resulted in less toxic deaths with similar outcome. Five-year EFS and OS of 18 patients with a non-DN medulloblastoma were 50.5 % (+/-11.8 %) and 60.6 % (+/-11.6 %), respectively [33]. The subsequent Head Start III trial was a prospective trial using intensive induction followed by one single course of myeloablative chemotherapy with autologous stem cell rescue. Sixty-five patients with classic (n = 52) and LCA (n = 13) medulloblastoma were included in the trial. The 5-year EFS and OS rates for patients with classic medulloblastoma were 26.6 % (+/-6 %) and 53 % (+/-7 %) and for patients with

**Table 6**
Summary of clinical studies undertaken in desmoplastic/nodular (DN) and MBEN infant medulloblastoma.

| Study | Number of Patients | Induction Chemotherapy | Marrow-ablative chemotherapy | Radiotherapy | Comments | Toxic Deaths | Event free survival (EFS) |
|---|---|---|---|---|---|---|---|
| HIT 2000 [30] | 42 (DN/MBEN) | HIT SKK + Intraventricular methotrexate | None | None | All M0 | None | 5 year PFS = 93 % |
| CCG −99703 [33] | 14 (DN/MBEN) | Etoposide, VCR, Cyclophosphamide, Cisplatin x 3 cycles followed by HD | Carboplatin + Thiotepa | None | 1 M1 | Not available as part of larger cohort | 5 year PFS = 78.6 % |
| ACNS1221 [27] | 25 | HIT SKK without intraventricular therapy | None | None | All M0 | None | 2 year PFS = 52 % SHH-II 2 year PFS = 66.7 % and SHH-I 2 year PFS = 30 % |
| SJYC07 [28] | 23 (SHH - DN/MBEN) | IV MTX, VCR, Cisplatin and Cyclophosphamide | None | None | All M0 | None | 5 year PFS = 51.1 % SHH-II 5year PFS = 75.4 % and SHH-I 5year PFS = 25.8 % |
| Headstart I/II/III [29,62] | 14 HS/II (DN/MBEN) 26 HS III (DN/MBEN) | Cisplatin, cyclophosphamide, etoposide, IV MTX, Vincristine, temozolomide for HSIII | Carboplatin/Thiotepa/Etoposide | None | M0–3 – 1patient M0 = 15 M 1–3 = 11 | HS I/II - 5 in overall study – unclear how many DN/MBEN HS III – 1 patient | HS I/II – 78.6 % HS III – 5 year PFS 89.6 % 5 year PFS M0 = 89.6 % 5 year PFS M+ = 82 % |

**Table 7**
Summary of clinical studies undertaken in non-desmoplastic infant medulloblastoma.

| Study | Number of Patients | Induction Chemotherapy | Marrow-ablative chemotherapy | Radiotherapy | Comments | Toxic Deaths | Progression on treatment | Event free survival (EFS) |
|---|---|---|---|---|---|---|---|---|
| **HIT-SKK'92** [65] | 23 classic MB | Three cycles Cyclophosphamide, HD MTX, vincristine, carboplatin, etoposide with intraventricular MTX | No | At progression or relapse | Multi-institutional study No randomization | 0 | 10 | 5-year PFS 34 % |
| **UKCCSG 9204** [66] | 6 classic MB M0 = 2; M1 + =4 5 LCA MB M0 = 3; M1 + =2 | Seven cycles Vincristine, Carboplatin, HD MTX, cyclophosphamide, cisplatin | No | 2 patients with classic MB had elective CSI; 3 pts with classic MB and 1 patient with LCA MB were irradiated at recurrence | Multi-institutional study No randomization | 0 | 9 | Classic MB 5-year EFS 33.3 % LCA MB 5-year EFS 0 % |
| **HIT-SKK 2000** [67] | 23 classic MB 3 Anaplastic MB All M0 | Three cycles of HIT-SKK Cyclophosphamide, HD MTX, vincristine, carboplatin, etoposide with intraventricular MTX Followed by two additional cycles without HD and intraventricular MTX | No | CSI 23.4 Gy with boost up to 54.6GY in case of noncomplete remission after chemotherapy and age > 18 y Local RT if age > 18 months | Multi-institutional study No randomization | 0 | NK | Classic MB 5-year EFS 30 % Anaplastic MB 5-year EFS 33 % |
| **COG P9934** [68] | 13 non desmoplastic/ nodular MB | Four cycles induction Cyclophosphamide, vincristine, cisplatin, etoposide Four cycles of maintenance course | No | age- and response adjusted focal radiotherapy to the posterior fossa (18 or 23.4 Gy) and tumor bed (50.4 or 54 Gy) | Multi-institutional study No randomization | 0 | NK | 4-year EFS 23 % |
| **SJYC07** [28] | 35 classic MB 6 LCA MB | Four cycles HD MTX, vincristine, cisplatin, cyclophosphamide. Risk adapted consolidation followed by six cycles of maintenance with oral cyclophosphamide, etoposide erlotinib | No | Risk adapted focal RT | Multi-institutional study No randomization | 0 | NA | 5-year EFS 10.6 % |
| **Head Start I/II** [60] | 12 classic MB All M0 | Five cycles Cyclophosphamide, Cisplatin, Etoposide, Vincristine | One course Thiotepa Etoposide Carboplatin | Irradiation only at relapse | Multi-institutional study | 4 | NA | 5-year EFS 42 % |
| **CCG−99703** [62] | 18 non-desmoplastic MB; M0 = 10; M1 + = 8 | Three cycles Cyclophosphamide, Cisplatin, Etoposide, Vincristine | Three cycles Carboplatin Thiotepa | No | Multi-institutional study | 2 | NA | 5-year EFS 50.5 % |
| **Head start III** [29] | 52 classic MB M0 = 18; M1 + =33 13 LCA MB M0 = 6; M1 + =7 | Five cycles of induction Cispaltin, Cyclophosphamide, Vincristine, Etoposode, HD MTX, Temozolomide | One course Thiotepa, Etoposide, Carboplatin | Based on age (if>6 y) and response (R+ post induction) Classic 8 pts LCA 2 pts | Non-randomized trial | 2 | PD during induction Classic 14pts LCA 5 pts | Classic MB: 5-year EFS 26.6 % LCA MB: 5-year EFS 38.1 % |

The vast majority of desmoplastic tumours are in the SHH subgroup and although the trial selection in most cases was based on the histology SHH subgroup is inferred.

LCA histology were 38 % (+/-13 %) and 46 % (+/-14 %), respectively. Ten patients received irradiation, of which 5 progressed. The 5-year radiation-free EFS for classic/LC/A medulloblastoma patients was 21 % (+/-5 %). These findings suggest that high-dose chemotherapy by itself might be enough to provide a cure for a subgroup of young patients with classic/LC/A medulloblastoma [29].

Importantly, prospective assessment of iMB therapy, in the context of contemporary molecular sub-classification, has not yet been formally evaluated within clinical trials; similarly, the relationship of molecular features to outcome remains to be determined. In addition, no randomised controlled trials have yet definitively assessed the benefit of high-dose chemotherapy in non-DN medulloblastoma. Most studies to date have been performed in small numbers of iMB patients. Looking forward, molecularly-informed trans-continental studies will be essential to yield to definitive clinically-actionable findings, to improve practice for these rare tumour groups.

### *1.11. Residual disease as a high-risk feature*

Extent of surgical resection is no longer considered as a prognostic variable in medulloblastoma. In the largest randomised trial so far reported for non-metastatic medulloblastoma patients, the 15 patients with post-operative residual disease (> 1.5 $cm^2$) did not have a significantly worse prognosis than the others [42]. In the St Jude medulloblastoma-96 trial the "high" risk group represented by those 6 patients having only residual disease (non-metastatic) reported having 100 % EFS/OS [12] The presence of residual post-operative disease was prognostic in the HIT-SIOP-PNET4 trial [35], but more recently, prognostic analyses on 184 medulloblastoma cases treated on HIT (German speaking countries cooperative group) protocols did not reveal a role for residual disease in a multivariate evaluation [70]. In an analysis of 125 consecutive patients in a single Italian institution, the 8 children having only residual disease did not have a statistically different EFS and OS from the patients without residual disease [71]. A recent report from the Paediatric Oncology Group (POG) 9631 protocol exploring the role of

concomitant oral etoposide during craniospinal irradiation again did not find residual disease as prognostic factor [72]. Most recently, a study of 1110 patients with medulloblastoma showed that residual disease alone (ie. as a sole risk-factor) is not prognostic [59], irrespective of the treatment received.

Considering all these data together, it is felt that there is a paucity of evidence to support the hypothesis that intensifying therapy to the craniospinal axis improves local control in the setting of a subtotal resection without the presence of other established high-risk factors. It is recommended that cases where residual tumour is the only 'high-risk' factor, and 'second-look' surgery may not be feasible or is not indicated due to other reasons, should be treated as per standard-risk disease.

### *1.12. Late-effects*

Current multi-modal therapies for medulloblastoma carry a high-risk of debilitating long-term toxicity [73] (Table 8). This is particularly significant for patients receiving surgery and CSI, but is also true for infants, despite their generally not receiving radiotherapy as part of their treatment.

Considering long-term toxicity due to CSI, age plays a critical role. Cognitive decline is variable but in generally is inversely proportional to the age of the patient and tends to become increasingly evident over several years. Neurocognitive outcomes focus on global cognitive dysfunction as well as problems with attention, working memory, executive functioning and processing speed, all of which attribute to the slower rate of cognitive development and educational attainment [43].

Second malignant neoplasms (SMNs) are a further major complication of treatment, particularly radiotherapy, given in childhood [74]. These occur in approximately 5 % of children [74] and young people treated for medulloblastoma and is higher for those having a combined chemo- and radiotherapy approach, than for those having radiotherapy alone. Data for those children having proton beam radiotherapy are not yet available, although theoretically should be lower as there is less radiation to organs other than the CNS. Other toxicities include endocrine dysfunction such as growth hormone deficiency (the most frequent sequelae) followed by thyroid dysfunction and disorders of puberty [44]. Bone growth, cardiac and vascular toxicity, with an increased frequency of stroke and coronary artery disease, have also been observed.

Survivors are also at risk for visual impairment due to cataract or visual damage due to raised intracranial pressure at diagnosis and regular ophthalmologic follow-up is required. Hearing loss, often known as the "invisible disability", is frequently observed because of platinum-based therapies and cochlear radiation [75].

There has been a general move towards proton beam radiotherapy to minimize the late effects of radiotherapy although a detailed discussion of this is beyond the scope of this paper.

Both the survivor and providers need to be aware of the survivor's treatment history, to prioritise health screening and intervention. It is suggested that all patients have an individual end of treatment summary completed, which includes the late effects risks and schedule of suggested follow-up monitoring.

**Table 8**
Table of late effects which may be seen in children and young people treated for medulloblastoma (adapted from Parkes et al. [69]).

| Toxicity | | Investigation |
|---|---|---|
| Endocrine | Hypothyroidism (Primary/Secondary) | Serum Free T4/TSH |
| | Growth hormone insufficiency | Growth chart showing crossing of growth centiles, IGF−1 and stimulation testing |
| | Hypoadrenalism | Early morning (pre−9.30 am) cortisol synacthen testing |
| | Delayed puberty | Clinical examination, serum LH/FSH, testosterone or oestradiol |
| | Infertility | Clinical examination, serum LH/FSH, testosterone or oestradiol, sperm testing when required or more specialised testing |
| Neurocognitive dysfunction | | Neurocognitive assessment |
| Hearing loss | | Auditory assessment |
| Neurological sequelae | | Clinical examination |
| Diplopia | | Clinical examination |
| Cataracts | | Clinical examination |
| Optic atrophy | | Fundoscopy, visual acuity |
| Vascular problems (e.g. Moya-Moya, arteritis, cavernoma) | | Usually manifests as a CVA (cerebro-vascular accident) or MRI follow up |
| Secondary tumours | | Suspicion on clinical examination or MRI follow up |

## 2. Standard recommendations

### *2.1. Medulloblastoma diagnostic criteria*

#### *2.1.1. Imaging*

Pre-operative imaging should be as per the SIOPE radiology guidelines [76]; whole brain and spine MRI imaging including the entirety of the dural sac, ideally using the sequences specified in the guidelines. Post-operative MR imaging within 72 hours of surgery should also be performed to assess residual disease post-surgery. If spinal imaging was not performed pre-operatively as recommended, this should be performed post-operatively. Where there is ongoing doubt, the spinal MRI should be repeated after 2 weeks for clarification (to minimise post-surgical blood products and dural enhancement that might confound imaging interpretation).

Staging including CSF staging is described using the Chang grading system [77], M0 No evidence of gross subarachnoid or hematogenous metastasis, M1 Microscopic tumour cells found in cerebrospinal fluid, M2 Gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space or in the third or lateral ventricles, M3 Gross nodular seeding in spinal subarachnoid space and M4 Metastasis outside the cerebrospinal axis.

#### *2.1.2. Histopathology*

A histopathological diagnosis of the medulloblastoma should be made to WHO (2021) criteria [1,2] by neuropathologists experienced in evaluating paediatric brain tumours. This can be achieved in the context of central pathology review. If available, samples should be assessed by H&E, silver impregnation (reticulin staining) and a CNS embryonal tumour immunohistochemical panel including synaptophysin, NeuN) GFAP, OTX2, YAP1, GAB1 or p75-NGFR, beta-catenin, p53, INI1, BRG1 as well as proliferation marker Ki-67 [78]. Once the histological diagnosis of medulloblastoma (including histological type and molecular type prediction) is confirmed, the molecular diagnostic panel should be activated as soon as feasible [79].

Desmoplastic/nodular (DN) medulloblastomas are defined by the admixture of reticulin free pale islands of better differentiated neoplastic cells and an extra-nodular reticulin rich component, where the tumour cells appear relatively more atypical with higher proliferative activity. In these internodular areas, markers of SHH activity are strongly expressed (YAP-1, p75-NGFR). Medulloblastoma with extensive nodularity (MBEN) are histologically similar to DN-MB but with marked expansion of the reticulin-free nodules which contain neurocytic differentiated neoplastic cells with strong nuclear NeuN expression within abundant neuropil, sometimes in a streaming and even linear pattern. DN-MB and MBEN do not express OTX2 and should be differentiated from classic-biphasic MB, which have focal nodularity in the absence of desmoplasia. Foci of desmoplasia related to large blood vessels and meningeal infiltration should not be interpreted as representing a desmoplastic component of DN-MB and MBEN tumours [1,2].

The large-cell/ anaplastic (LC/A) medulloblastoma variant is defined by the presence of cells with severe cytological anaplasia and/or large-cell morphology (monomorphic cells with round nuclei with large

nucleoli) within a large proportion of cells (>50 % of area). The determination of severe cytological anaplasia is defined by a high degree of nuclear enlargement, pleomorphism, nuclear moulding and wrapping of cells, higher mitotic activity and widespread apoptosis [1,2].

#### 2.1.3. Molecular pathology

Molecular pathology assessments should be performed according to national policy and accreditation requirements for clinical molecular diagnostics. Analysis should be undertaken and reported using standard validated methods in laboratories accredited to national standards.

#### 2.1.4. Molecular typing

Diagnosis of the molecularly defined medulloblastoma types should be undertaken according to the current WHO classification of CNS tumours. The current (2021) classification defines the following types [1,2]:

- WNT-activated
- SHH-activated/*TP53* wildtype
- SHH-activated/*TP53* mutant
- non-WNT/non-SHH (including the previously defined Group 3 and Group 4 principal molecular groups and their subgroups).

It is recommended that assignment to molecular type should be based on at least two independent validated methods. In addition to the definition of the molecularly-defined medulloblastoma entity by IHC, molecular testing for this assignment should be undertaken on extracted tumour (DNA or RNA) using a validated molecular method.

Methods for molecular classification should be based on DNA methylation or transcriptomic profiling, and DNA sequencing (e.g. *CTNNB1* in WNT, *TP53* sequencing in SHH medulloblastoma; see next sections). Methods which have been used in clinical diagnostics include Illumina 850 K/EPIC DNA methylation array, MS-MIMIC MassArray assay, [80] Nanopore sequencing and Nanostring technology. In addition, epigenetic SHH subtypes 1–4 [2,17,19,20] and non-WNT/non-SHH subtypes –1–8 [2,18]. may be optionally assigned using molecular methods described above, however these do not currently influence patient management.

### 2.2. Assessment of specific cytogenetic copy number alterations (MYC, MYCN, chromosome 6 status)

Specific genetic alterations should be assessed by iFISH, array-based or other methods. iFISH is the 'gold standard' method for detection of gene amplification and should be carried out using commercial FISH probes to assess copy numbers of *MYC* and *MYCN* in relation to centromeric reference probes, and to assess monosomy 6 status. Two hundred nuclei should be counted and *MYC* or *MYCN* amplification-positive cases are determined as those with $\geq$ 5 % of nuclei showing evidence of gene amplification (signals consistent with double minute or homogenously staining region formation, and test probe copy number $\geq$ 4 times copy number of the reference signal) [22]. For monosomy 6 status, 200 nuclei should be counted, and positive cases are determined as those with $\geq$ 50 % of nuclei showing a single signal for both the p- and q-arm probes (i.e. 1:1). To avoid false positive calling, array methods are also recommended for the detection of whole chromosomal (arm) alterations such as monosomy 6.

Other methods (e.g. SNP array, whole-genome sequencing) may be used, however false-negatives due to low numbers of amplified cells are a particular concern and their use is only recommended following validation of their performance against iFISH [79].

### 2.3. Mutation analysis

Assessments should be undertaken by direct sequence analysis of DNA extracted from tumour and blood (white blood cell) material.

Genes for analysis in tumour samples currently include:

***CTNNB1:*** Analysis should encompass the mutation cluster region in exon 3, including sequences encoding amino acids 30–45. Positive results are those cases displaying confirmed non-synonymous missense mutations or small in-frame deletions in this mutation cluster region.

***TP53, SMO, PTCH1, SUFU, ELP1, GPR161:*** Analysis of the whole coding sequence and splice sites to be undertaken in SHH activated tumours. Positive results are those cases displaying confirmed non-synonymous variations to the coding sequence.

***APC:*** Analysis of the whole coding sequence and splice sites to be undertaken in cases of *CTNNB1*-wildtype WNT medulloblastoma patients. Positive results are those cases displaying confirmed non- synonymous variations to the coding sequence.

***BRCA2, PALB2:*** Fanconi-type mutations should be assessed in all patients' tumours by analysis of the whole coding region and splice sites. Positive results are those cases displaying confirmed non-synonymous variations to the coding sequence.

### 2.4. Evaluation of germline alterations

In all cases with SHH medulloblastomas or *CTNNB1*-wildtype WNT medulloblastomas, genetic counselling of the patients and their families should be offered immediately, and germline testing performed in a laboratory certified for genetic testing of germline material.

In cases with somatic *TP53, PTCH, SUFU, APC, PALB2, BRCA2, ELP1* or *GRP161* mutations, these mutations should be indicated to a human geneticist responsible for genetic counselling and testing. The presence in the germline should be tested, using DNA extracted from the patient blood sample.

### 2.5. Reporting of variants

Variants (at the nucleotide and amino acid level) should be recorded and referenced according to the international nomenclature (http://www.hgvs.org/mutnomen/). Variant allele frequencies should be recorded.

### 2.6. Cerebrospinal fluid (CSF)

CSF (via a lumbar spinal tap) should be collected and the presence of medulloblastoma cells looked for. The use of immunocytochemistry with medulloblastoma-associated markers is highly recommended to be able to detect single tumour cells in the specimen. This should ideally be performed at 14 days post operatively, but if performed before this date with no evidence of malignant cells it need not be repeated. However, if positive prior to 14 days post- surgery, the sample must be repeated at a minimum of 14 days post-surgery. Criteria for refining M1-stage via a central reference centre have been elaborated by the HIT group [81].

Following the investigations outlined, the individual diagnosis and risk-group may be determined, and treatment planned accordingly (Tables 1 and 2). Treatment recommendations are outlined below.

With the increasing ability to gain useful biological information from both CSF [82] and plasma it is important to store samples for future analysis in a biobank. This is equally important for tumour samples as biological investigation form the foundation of biological discovery which are used in risk stratified trials.

## 3. Treatment

Fig. 1 outlines the suggested treatment schema for medulloblastoma

It should be pointed out that despite the ever more detailed biological analysis available, it is not possible to have trials for each individual subgroup or biological finding, due to the relative rarity of the disease groups; tumours are therefore grouped in risk groups and treated accordingly. Care must be taken not to adopt experimental arms from trial protocols into routine practice, prior to trials' results being

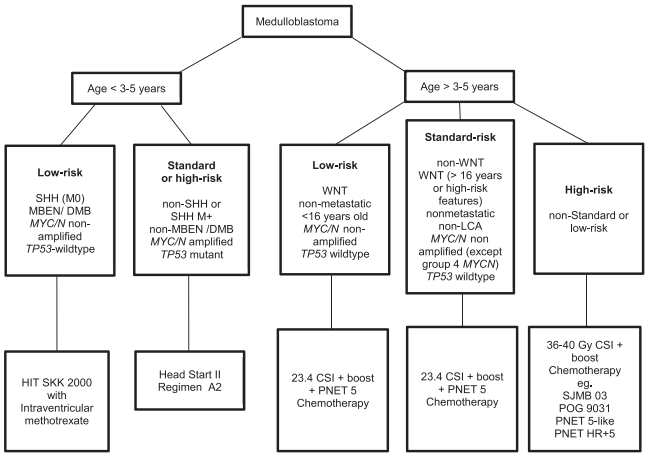


**Fig. 1.** Overall treatment schema for children with medulloblastoma.

available as safety and efficacy will not have been established and this approach may do the patients harm or affect their outcome.

### 3.1. Surgery

Surgical resection remains the mainstay of the initial management of medulloblastoma. Resection allows confirmation of tissue diagnosis, decompresses the posterior fossa, and, in particular, the brainstem, and in most cases facilitates resolution of mostly non-communicating hydrocephalus at diagnosis.

As in other tumours arising in the posterior fossa, medulloblastomas are often associated with a degree of hydrocephalus on presentation. The need for urgent CSF diversion is dictated by the severity of the hydrocephalus on imaging and the clinical condition of the child. The Canadian preoperative prediction rule for hydrocephalus attempts to predict the need for CSF diversion pre- and post-operatively [83]. The most important factors are age under two years (3 points) and the presence of cerebral metastases (3 points), followed by radiologically moderate or severe hydrocephalus (2 points) and the presence of papilloedema, or transependymal oedema in the modified version (1 point) [83,84]. An additional point is given for suspected medulloblastoma. Children with a low score, defined as under 5, out of a total of 10, may be observed carefully, and can usually undergo resection of the tumour on the next available operating list under corticosteroid cover. In children with a high score, or clinical signs of hydrocephalus, an external ventricular drain or an endoscopic third ventriculocisternostomy may need to be considered before resection. As hydrocephalus resolves after resection in up to 70 % of children, pre-operative insertion of a ventriculoperitoneal shunt is not recommended. Children who develop hydrocephalus post-operatively may still be considered for endoscopic ventriculocisternostomy in cases with the non-communicating type of hydrocephalus, if not already performed before tumor surgery. However, especially in cases with disseminated disease or perioperative complications like haemorrhage, infection is likely to require a shunt. Early consequent decisions are essential to avoid any delay to adjuvant therapy.

Surgical resection typically involves a posterior fossa craniotomy, with exposure of the tumour within the fourth ventricle either through a trans-foramen Magendie, transvermian or telovelar approach. Once the anatomy of the tumour and its relationship to eloquent structures is defined, the mass is usually microsurgically debulked using an ultrasonic tissue aspirator or suction in combination with diathermy. Tumour adherent to the fourth ventricular floor is reduced as much as possible, taking care not to damage the surface of the brainstem. In addition, the dentate nucleus and the associated dentato-thalamic pathways within the medial and superior cerebellar peduncles must be preserved. Most of these tumours are highly vascular; early control of large arterial pedicles, which usually arise from distal cortical branches of the posterior inferior cerebellar arteries as well as relevant veins often draining towards bilateral outflow vasculature, is beneficial, particularly in small children and infants. Some medulloblastomas are primarily located within the cerebellar vermis or hemispheres. These are easier and safer tumours to resect, as their interface with the brainstem is more limited. Recovery from cerebellar surgery is typically more rapid in the latter category.

Despite ongoing surgical progress, the neurological morbidity of fourth ventricular tumour resection remains at a relevant rate. In a recent study reviewing 167 fourth ventricular tumours, from one institution, recruited over 15 years, having excluded 169 non-midline posterior fossa tumours, the overall rate of cerebellar mutism remained fairly constant (overall 28.7 %) throughout the recruitment period. However, the use of intraoperative ultrasound was associated with a significantly reduced rate of postoperative CMS [85]. The latter factor might also be influenced by center experience which was shown to reduce CMS rate in a US American cohort [86]. The rates of new post-operative cranial neuropathy and new ataxia and gait abnormalities were 18 % and 12.6 % respectively. In the Nordic Cerebellar Mutism Study, which evaluated 426 patients from 26 centres in 10 European countries in 376 individuals, postoperative speech status was evaluated. The study showed a cerebellar mutism rate of 14.1 % and additional reduced speech status of 15.7 %. After 80 days of follow up from 36 patients in which data was available, 4 individuals remained mute [87]. Surprisingly, both studies demonstrated that the use of the telovelar approach, rather than the transvermian route which requires some vermian resection and was therefore always thought to be more harmful, does not significantly reduce the incidence of cerebellar mutism. An MRI tractography study in a series of paediatric controls has demonstrated that the components of the dentato-rubro-thalamic tracts that preferentially project to the pre-motor cortex are mostly situated on the medial side of the superior cerebellar peduncles, and therefore most likely to be injured during resection of a fourth ventricular tumour [85]. Whether protection of this region results in a reduced rate of mutism remains to be explored.

The current surgical consensus is to pursue a maximal safe resection [3,59–61]. Most trials and publications have categorised extent of resection into gross total resection (GTR), where no tumour is evident on post-operative MRI scans, typically obtained within 72 hours of surgery, near-total resection (NTR) where there is residual tumour visible on the post-operative MRI scan that is less than 1.5 $cm^2$ at its widest extent, and subtotal resection (STR), where the residual tumour is larger than 1.5 $cm^2$.

Although residual disease is not an independent variable for prognosis it remains the recommendation that maximal safe resection is the desired surgical outcome in order to maintain the current cure rates.

### 3.2. Radiotherapy

Radiotherapy is a fundamental element in the management of children aged > 3–5 years with medulloblastoma, and postoperative craniospinal radiotherapy (CSI) is considered the cornerstone of curative treatment. Despite advances in systemic therapy and neurosurgical techniques, CSI remains the standard radiotherapy technique. Conventionally, children with MB are categorized post- operatively as favourable-risk (WNT activated tumours −10 % of patients) standard-risk (56 % of patients) or high-risk (those with M+ disease, *MYC or MYCN* (bar group 4) amplification, large cell /anaplastic histology - 34 % of patients) although these risk groups are continuously being refined (see above).

With modern multidisciplinary management, more than 80 % of children with standard-risk medulloblastoma (SR-MB) and up to 70 % of children with high-risk medulloblastoma (HR-MB) are long-term survivors. Current clinical trials are evaluating risk-adapted radiotherapy in

favourable-risk medulloblastoma (LR-MB) to reduce long-term sequelae, whereas the research approach in HR-MB is to improve clinical outcomes with dose-intensification of chemotherapy and the use of hyperfractionated radiotherapy regimens.

Technological advances such as tomotherapy, VMAT, and proton therapy may further improve the therapeutic ratio by reducing long term radiotherapy toxicities [88]. Most countries are moving towards proton beam radiotherapy when it is available, due to its more favourable toxicity profile.

### 3.3. Timing

Available evidence indicates delay of radiotherapy beyond 49 days after surgery is associated with inferior outcomes [35]. The aim should therefore be for radiotherapy to start within 28 days of surgery and no later than 40 days after surgery (especially standard-risk disease where pre radiotherapy chemotherapy is not routinely used.

### 3.4. Overview

The CSI component of treatment is planned and administered either in 3D technique, VMAT or proton therapy; however, irradiation of the primary site boost after CSI should be preferentially delivered using a VMAT technique or proton therapy in order to minimise the dose to the temporal lobes.

### 3.5. Target volume definitions

**Craniospinal Irradiation (CSI):** The CSI volume includes the entire subarachnoid volume with special attention given to include the cribriform plate, pituitary fossa, middle cranial fossa and temporal fossa intracranially and the inferior aspect of the thecal sac (defined on the pre-operative MRI and usually up to S2/3). The full width of the spinal subarachnoid space should be included.

**Tumour Bed Boost -** Gross Tumour Volume (**GTV**): The GTV includes all gross residual tumour and/or the tumour bed at the primary site based on the initial pre-operative MRI that defines the tissues initially involved with disease anatomically and the postoperative and pre-irradiation MRI that identify residual disease defined on the T1 gadolinium and T2/ T2 flair weighted images due to possible heterogenous characteristics of the tumour) and/or the tumour bed. The GTV in most cases will be a contracted or collapsed tumour bed. Tissue defects resulting from surgical approaches will not be included as part of the GTV when not previously involved by tumour.

Tumour Bed Boost - Clinical Target Volume (**CTV**): The CTV includes the GTV with an added margin that is meant to treat subclinical microscopic disease and is anatomically confined (i.e. the CTV is limited to the confines of the bony calvarium, falx and tentorium where applicable or extends up to but not beyond neuroanatomic structures through which tumour extension or invasion is certain not to have occurred); the CTV margin is currently 0.5–1 cm for all patients. When the GTV approaches the boundary of an anatomic compartment, the CTV will extend up to and include the boundary.

## 4. Dose

### 4.1. High-risk Medulloblastoma

Craniospinal irradiation (CSI) dose is currently given as 36 Gy in 20 fractions. The boost to the tumour bed is 18 Gy in 10 fractions. The total dose of the planning target volume (PTV) is 54 Gy for photon radiotherapy. Sites of brain or spinal metastasis (M2 & M3) also receive a boost from 45 Gy to 50.4 Gy (if felt appropriate) or dependent on trial requirements or response to chemotherapy.

In the SIOP HRMB trial, hyperfractionated and accelerated radiotherapy is used for high-risk disease with two fractions of 1.3 Gy daily, five days per week in 15 days with an additional 8 days boost to the posterior fossa [25]. The total dose to the primary site is 59.8 Gy with boosts to the metastatic sites in the brain being 20.8 Gy total dose, (1.3 Gy/fraction, 2 fraction/day for 8 treatment days with a total dose to the brain metastasis of 59.8 Gy. For spinal metastasis the boost is 7.8 Gy total dose (1.3 Gy/fraction, 2 fractions/day 3 for treatment days) with a total dose given to spinal metastasis of 46.8 Gy.

### 4.2. Standard-risk Medulloblastoma

Craniospinal axis: Phase 1; 23.4 Gy in 13 fractions and phase 2; 30.6 Gy in 17 fractions to boost tumour bed. Total dose to boost PTV is currently 54 Gy.

Modifications to treatment may be necessary due to hematological toxicity.

Due to the poor survivorship outcome for non-SHH infant tumours, dose adapted radiotherapy may be used and is currently under consideration for an international SIOPE clinical trial.

### 4.3. Favourable-risk Medulloblastoma

Although preliminary results from SJMB 12 suggest reducing radiotherapy dose in this group [41] does not result in an increased relapse rate, evidence from other trials (eg SIOP-PNET5-MB) will be necessary before recommending a reduction in radiotherapy dose in routine practice.

### 4.4. Chemotherapy

Chemotherapy has been shown to be a valuable addition alongside surgery and radiotherapy in treating medulloblastoma. In the very young where radiotherapy is not used due to the devastating neurocognitive consequences it is used as the sole non-surgical treatment modality. Chemotherapy can either be used prior to radiation, during radiation or as consolidation post radiotherapy, these options will be discussed below.

### 4.5. Low-risk infant Medulloblastoma

iMB patients under 4 years of age with wild-type *TP53* and *MYCN* non–amplified histological DM/MBEN tumours without metastatic disease may be treated in one of 2 ways which give similar results and are the basis of an upcoming transatlantic trial [29,65]. The 2 recommended protocols are HIT SKK (as per HIT 2000) with intraventricular methotrexate or a HeadStart protocol. The European current recommendation is to use the HIT SKK approach. These approaches are used for those that have a low risk of needing future radiotherapy as the combination of radiotherapy and intraventricular methotrexate has significant neurocognitive consequences. Patients with low risk iMB will receive 3 cycles (5 if residual disease) of HIT SKK chemotherapy as per HIT2000. Systemic chemotherapy should commence at the latest within 28 days of surgery. Systemic chemotherapy should not be delayed allowing for the insertion of Ommaya/Rickham reservoir if HIT SKK chemotherapy is used. If there is an indwelling VP shunt then it should have a magnetic on/off valve to allow intraventricular methotrexate administration. Patients with residual tumour after 5 cycles of chemotherapy should be discussed with international coordinators and re-evaluated for second look surgery.

Patients receive 3 cycles (5 if residual disease after 3 cycles) of systemic chemotherapy according to HIT 2000 (Fig. 2). The first 3 cycles contain systemic and intraventricular methotrexate. Intraventricular chemotherapy will be administered via an Ommaya/Rickham reservoir (see Appendix 1)). For those young children with metastatic disease, the HeadStart protocol is recommended. Children should also be tested for PTCH (Gorlins) /SUFU germline mutations.

SIOPE does not support the routine use of intrathecal methotrexate

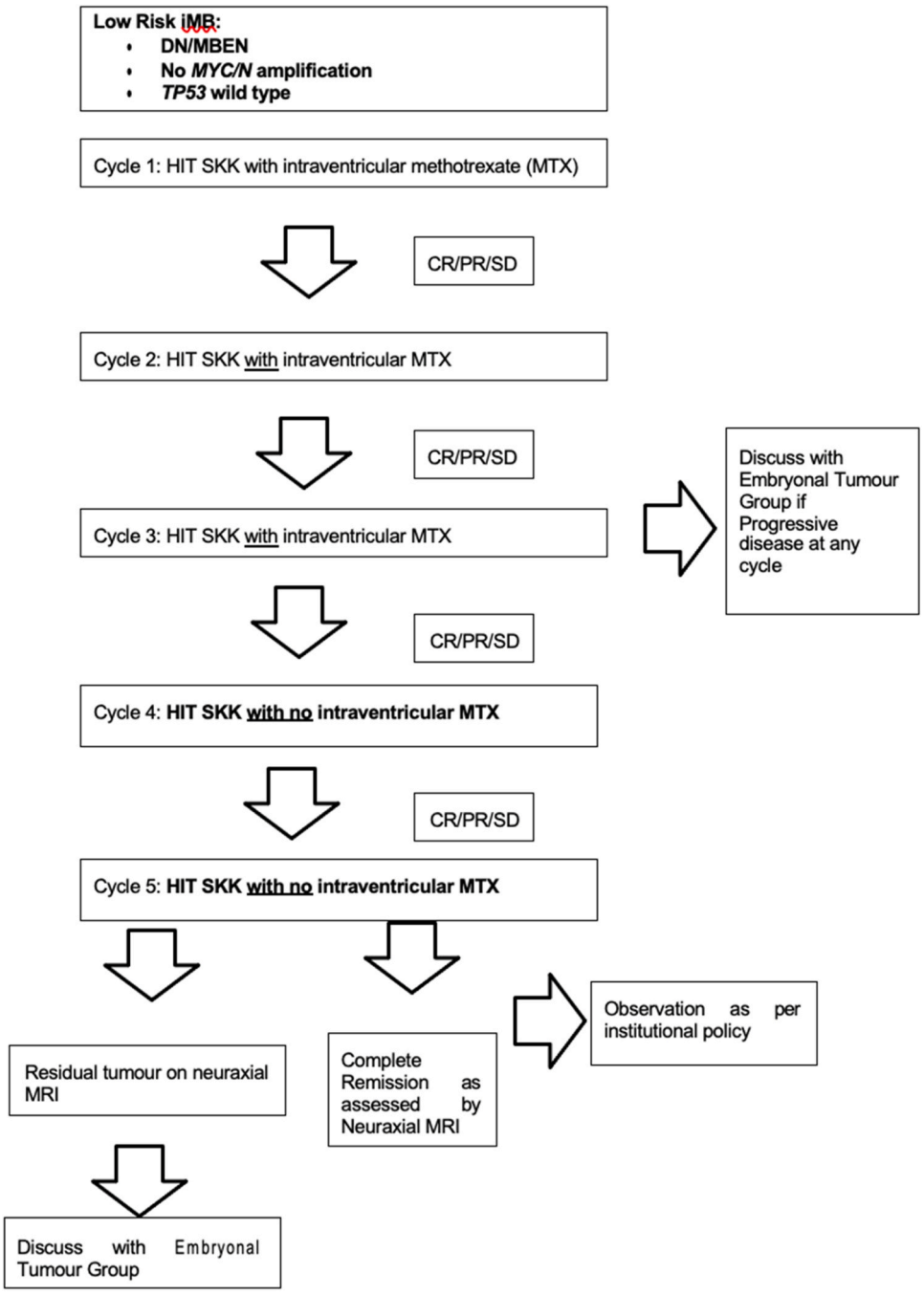


**Fig. 2.** Algorithm for treatment of Low-Risk Infant Medulloblastoma.

administered by lumbar puncture/port for the treatment of patients with infant medulloblastoma in this guideline.

### *4.6. Standard and high-risk infant Medulloblastoma (age < 3–5 years)*

**Induction chemotherapy:** The European recommendation for patients with standard and high-risk infant medulloblastoma is to receive 5 cycles of intensive induction chemotherapy in accordance with Head Start II Regimen A2 [89] (Fig. 3). Chemotherapy should aim to start at the latest within 28 days after surgery. The cycles should be given every 21–28 days.

**Stem cell collection:** This should be undertaken as per local policy. There is no particular guidance for stem cell collection following induction chemotherapy. Cold harvest with GCSF prior to commencing induction chemotherapy or after 5th cycle of induction chemotherapy is acceptable. Children considered ineligible for stem cell collection should be discussed with the SIOPE CNS Embryonal Tumour Group.

Second look surgery should be considered if clinical remission has not been achieved after induction chemotherapy and the tumour is amenable to further surgery. Consolidation with high dose chemotherapy (Carboplatin, Etoposide and Thiotepa) and autologous stem cell rescue should take place in patients who have not progressed during the induction phase of therapy.

**Supportive care during induction chemotherapy for standard and high-risk Medulloblastoma:** Steroids for anti-emesis must be avoided (hydrocortisone replacement as required). This chemotherapy is highly emetogenic and aggressive anti-emetics upfront are essential. Drugs that may interact with methotrexate and nephrotoxic drugs

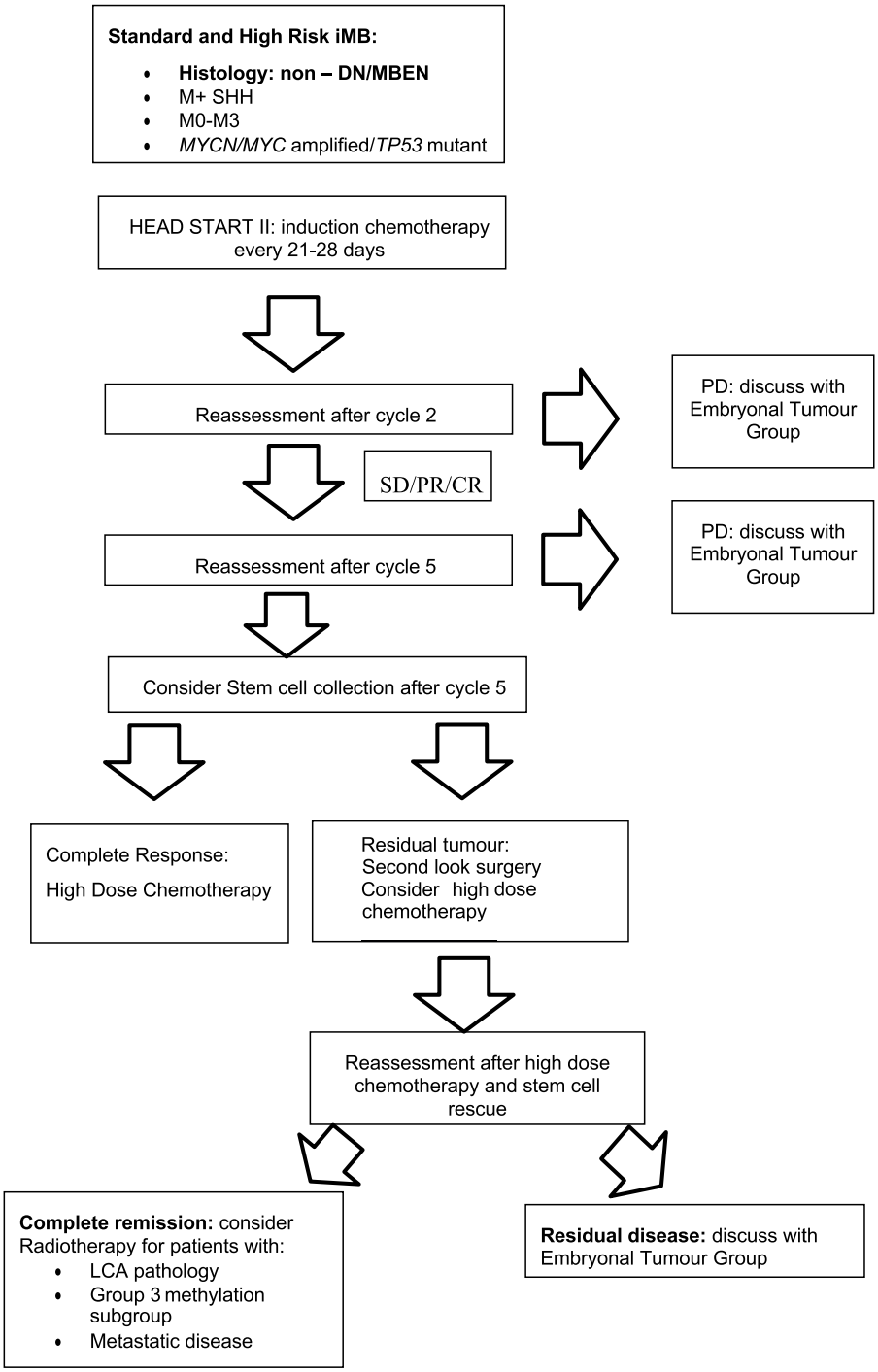


**Fig. 3.** Algorithm for treatment of standard and High-Risk Infant Medulloblastoma.

should be avoided as per local guidance. (see appendix 2)

**High dose chemotherapy (HDC) with autologous stem cell rescue (ASCR):** Following completion of induction chemotherapy, if there is radiographic evidence of residual tumour on disease evaluation, second-look surgery (SLS) should be considered. Second opinions should be sought from national neurosurgical leads. Post-SLS, or if SLS not deemed safe/possible, the patient should proceed to consolidation myeloablative chemotherapy. These patients should be discussed with the Embryonal Tumour Group with regards possible irradiation following recovery from the consolidation chemotherapy.

High-dose chemotherapy should start 3–4 weeks after the last course of intensive induction chemotherapy if there no evidence of progressive disease.

### *4.7. Standard and Favourable-risk Medulloblastoma (Age > 3–5 years)*

The recommended chemotherapy for standard and favourable-risk medulloblastoma (M0 WNT activated tumours under 16 years of age) is as per the PNET 5 protocol. This does not include vincristine during radiotherapy which should be 23.4 Gy CSI + boost until the trials using reduced radiotherapy for favourable-risk disease (18 Gy) have been reported.

Chemotherapy is alternating courses of cyclophosphamide (1000 mg/m$^2$ x 2 and vincristine (1.5 mg/m$^2$) with cisplatin (70 mg/

$m^2$), CCNU (75 mg/$m^2$) and vincristine (1.5 mg/$m^2$) for a total of 8 courses. Details can be found in appendix 3.

### 4.8. High-risk medulloblastoma (Age > 3–5 years)

There are several potential regimens (see Table 5) which when the biology is accounted are likely to give similar results. The European recommendations are based on the use of protocols across Europe. The four protocols that are most commonly used are:

**1.SJMB 12 protocol:** (4 courses of cyclophosphamide (1.5 g/$m^2$ x 2), cisplatin (75 mg/$m^2$) and Vincristine (1.0 mg/$m^2$).

**2. POG 9031:** Induction consists of cisplatin 90 mg/$m^2$ (day 1) followed by etoposide 150 mg/$m^2$ on day 3 and 4. Two cycles are given 4 weeks apart. Consolidation therapy consists of 7 cycles of cyclophosphamide 1000 mg $m^2$ on day 1 and 2 and vincristine 2.0 mg/$m^2$ on day 1 (maximum dose 2.0 mg)

**3. Standard PNET 5 like chemotherapy**: As described above.

**4. PNET HR+ 5**: Two courses of carboplatin and etoposide induction followed by twin thiotepa high dose therapy with stem cell support with oral temozolomide following radiotherapy (as per Arm C in the SIOPE HRMB trial) [25].

As described above, the high-risk SIOPE medulloblastoma trial for high-risk medulloblastoma (SIOP-HR-MB), currently open in many European countries, will assess relative efficacies of different chemotherapy and radiotherapy regimens [25].

### 4.9. Summary

This paper outlines the evidential background of medulloblastoma treatment, and the current suggestions for treatment and stratification endorsed by SIOP-Europe. Details of contemporary biological evaluations, associated methods/approaches, and their use for practical diagnostics and risk-stratification are described, alongside treatment details.

The field is ever moving as new evidence becomes available, and risk groups as well as treatment will be revaluated when trial results become available. Finally, the outcome for relapsed children following upfront CSI remains very poor; a separate paper is planned which will describe suggested therapies and management approaches for relapsed medulloblastoma.

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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.2024.100205.

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