CLINICAL PRACTICE RECOMMENDATIONS

Medulloblastoma

Clinical Recommendation for the treatment of Children and Young People with Medulloblastoma outside of a trial setting.

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This document is to provide guidance and recommendations for the treatment of medulloblastoma. However it is preferable for children to be enrolled on clinical trials whether they are international trials, national or institutional ones.

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1. BACKGROUND

Medulloblastoma (MB) 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. The following variants of medulloblastoma are recognised in the World Health Organisation (WHO) classification of Central nervous system (CNS) tumours (2016). (1)

Medulloblastoma, genetically defined

- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated and *TP53*-mutant
- Medulloblastoma, SHH-activated and *TP53*-wildtype
- Medulloblastoma, non-WNT/non-SHH Medulloblastoma (encompassing Group 3 and Group 4)

Medulloblastoma, histologically defined

- Classic medulloblastoma,
- Desmoplastic/nodular medulloblastoma
- Medulloblastoma with extensive nodularity
- Large-cell / anaplastic medulloblastoma

Our understanding of these variants, and their clinical relevance is evolving and altering our understanding of prognosis and risk and are creating a shifting scope of disease stratification. (2–4) Although risk stratification is in constant evolution the table below outlines the current thinking.

Table 1. Risk groups for children age 3-5 years old and over.

	Molecular features	Histology	Residual	Metastatic disease
Low Risk	WNT subgroup under 16 years old TP53 wild type, MYCN not amplified	Classic, Nodular Desmoplastic	<1.5cm^2	M0
Standard Risk	TP53 wild type, MYCN not amplified (unless group 4 MYCN amplified)	Classic, Nodular Desmoplastic	<1.5cm^2	M0
	WNT subgroup any age and not low risk	Any	Any	M+ if under 16 M0 if over 16
	No biological high-risk features non- WNT subgroup	Classic, Nodular Desmoplastic	≥1.5 cm^2	M0
High Risk	TP53 mutant and /or MYCN / MYC amplified (unless group 4 MYCN amplified)	Classic, Nodular Desmoplastic,	Any	Any
	Any	Classical	≥1.5cm2	M+
	Any non-WNT and WNT > 16 years	Any	<1.5cm2	M+
	MYC amplified	Any	Any	Any
	Any non-WNT	Anaplastic Large Cell	Any	Any

Table 2. Risk groups for children < 3-5 years

	Molecular features	Histology	Residual	Metastatic disease
Low Risk	SHH - TP53 wild type MYC/ MYCN not amplified	DN/MBEN	Any	Any
Standard Risk	Not high risk, non- SHH, non WNT	Classical	<1.5cm2	M0
High Risk	TP53 mutant and/or MYC/ MYCN amplified	DN/MBEN	Any	Any
	non- SHH, non WNT	Classical	≥1.5cm2	Any
	non- SHH, non WNT	Classical	<1.5cm2	M+
	MYC amplified	Classical	Any	Any
	Any	Anaplastic Large Cell	Any	Any

1.1 Biological and clinical risk groups.

The discovery of molecular disease subgroups within MB represents the most fundamental recent advance. Current international consensus recognises four subgroups – WNT, SHH, Group 3 and Group 4 (5) although a more recent paper suggests a 13 subgroup model. {Sharma}Each subgroup is defined empirically by genome-wide transcriptomic and DNA methylation patterns (4, 6) and characterised by distinct clinico-pathological and molecular features. WNT and SHH are synonymous with WNT (wnt/wingless pathway) and SHH (sonic hedgehog pathway) activating mutations respectively (7, 8). Childhood WNT patients (<16 years at diagnosis) consistently show a favourable prognosis (>90% survival) (9–13). In addition, significant biological heterogeneity is evident within each non-WNT subgroup, for instance *TP53* mutations associate with a poor outcome in SHH (4, 14). In contrast, Group 3 and Group 4 harbour few mutations but multiple DNA copy number alterations (8). Importantly, subgrouping and *TP53* status are now integral to the 2021 World Health Organization (WHO) MB classification and are considered 'standard-of-care' (1).

Familial disease/germline mutations describe a notable proportion of MBs (5-10%); predominantly Gorlin (*PTCH1/SUFU* mutation in SHH patients), Turcot (Adenomatous-polyposis-coli -Protein *(APC)* in WNT patients), Li-Fraumeni (*TP53* in SHH patients) and Fanconi's Anaemia (*BRCA2/PALB2*, subgroup unknown), and have been associated with systemic radio- and chemo sensitivity, and must also be considered in therapy selection (8).

In addition to WNT and SHH/TP53 mutated tumours, the presence of *MYC* or *MYCN* amplification (unless Group 4 MYCN) have been consistently identified as independent prognostic factors in trials-based studies (10, 12, 15). *MYC/MYCN* amplification is also significantly associated with metastasis and large cell/anaplastic (LCA) histology (15). Schema which incorporate these combined factors significantly outperform risk-stratification using clinical factors alone (4, 10, 12). The prognostic significance of *MYC/MYCN* amplification and histology is likely to be relevant only in the context of molecular subgrouping (e.g. *MYC* amplification in Group 3 tumours; *MYCN* amplification in SHH but not Group 4 tumours) and therefore clearer risk groups may become apparent as these associations are validated (4, 16). *MYCN* amplification was considered a 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 consensus molecular subgroups (12, 15). Two large retrospective studies have since been undertaken which have assessed the prognostic impact of *MYCN* amplification with reference to these subgroups (4, 16). In both, *MYCN* amplification was associated with the SHH and Group 4 subgroups and displayed different clinical outcomes 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 been validated in unpublished investigations of two groups of standard-risk patients (i.e. M-, R- with classic or desmoplastic pathology, and no evidence of *MYC* amplification) (17). Firstly, from the HIT-SIOP-PNET4 clinical trial cohort, *MYCN* amplification (by interphase fluorescence in situ hybridisation (iFISH), using SIOP-PNET5-MB criteria) was not observed in SHH (0/20) or Group 3 (0/15) patients, but was detected in 15% (11/74) of Group 4 patients. Within these Group 4 patients, five-year PFS of *MYCN* amplified patients was >90% and did not differ significantly (p=0.502, log-rank test) from non-amplified patients (17). Secondly, from a UK research cohort, including cases described by Schwalbe *et al.* (4), *MYCN*

amplification was found in 2/17 SHH, 0/17 Group 3 and 5/62 Group 4 patients. Within Group 4, PFS of *MYCN* amplified patients was 80% (4/5 patients) and did not differ significantly (p=0.544, log-rank test) from non-amplified patients (17).

Moreover, emerging biological risk factors have clear potential to further understand disease heterogeneity and improve the stratification of risk in HR-MB, and require urgent evaluation and/or validation in the clinical trials setting (e.g. novel molecular subgroups within Group 3/4 tumours (4), M+ in Group 4 tumours (3) which, in initial studies, can be used to differentiate favourable (>90% 5-year survival), standard risk (SR) (>75% 5-year survival) high risk and very high-risk (VHR);(<40% 5-year survival) disease groups within SIOP-HRMB).

LOW RISK

Medulloblastoma is a heterogeneous disease at the molecular level and risk stratification based on this should be considered.

Several studies globally both prospective and retrospective have shown that non-metastatic WNT patients under the age of 16 have an excellent survival independent of the protocol they have been treated with. For example, the prospective PNET3, PNET4 and SJMB96 studies have shown that non-metastatic WNT patients treated with surgery, radiation +/− chemotherapy have excellent survival rates. Although, as showed by PNET4, the same doesn't appear to apply for WNT patients over the age of 16, since they may not be a low-risk group (for instance, they were excluded from initial PNET5 MB protocol) (3).

Children with WNT medulloblastoma have by far the most favourable outcomes of all medulloblastoma subgroups. Subsequently, the newest generation of biologically-informed clinical trials, specifically PNET5 MB, SJMB12 and COG ACNS1422, are evaluating therapy de-escalation for patients with WNT tumours, in order to reduce therapy-related morbidity(3, 18).

Study	ClinicalTrial.gov Number	Phase	Treatment	Key features
PNET 5 MB	NCT02066220	II/III	Risk-specific radio- and chemotherapy	Low-risk: Reduced-dose craniospinal irradiation (18Gy) + 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	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)

Table 3. Trials including low risk medulloblastoma (adapted from Thompson et al 2020 (18))

1.2 Treatment of Standard Risk Medulloblastoma.

In studies from the last 2 decades in paediatric medulloblastoma, EFS and OS have slowly risen over this period of time, with multiple studies reporting 5-year EFS and OS rates of > 70% in children with non-disseminated disease at time of diagnosis.

Potential reasons for this improvement have been the routine employment of more aggressive surgery; more refined preoperative evaluations, resulting in a more pristine group of children with non-disseminated disease; and the use of adjuvant CT during and after RT(19) as well as improved radiotherapy techniques and equipment.

Therefore, the aim is to have a better identification of standard-risk patients, which has been made given the current condition of imaging and pathology, allowing a better stratification of these group of patients.

Over times, the concept of standard-risk has changed and has become more detailed, including clinical, biological and imaging aspects. Considering this, comparisons between studies may be difficult, however, the newly molecularly based stratification might also identify patients who will be amenable to treatment with even less aggressive therapy(19).

Currently accepted definition of standard-risk includes 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. Patients were to have < 1.5 cm^2 of residual tumour on postoperative imaging performed within 72 h of surgery (see section on residual disease below). Presently, 5-year overall survival (OS) for standard risk MB patients included in clinical trials is reported to be 80% (Table 4). At present, the tendency is to de-escalate therapy considering the acute and late-effects (mostly due to radiotherapy), provided staging and radiation therapy are performed under optimal conditions.

Table 4. Standard risk medulloblastoma trials.

Study	Number of	Radiotherapy dose	Definition of Standard Risk	Chemotherapy	Comments	Toxic Deaths	Progression on treatment	Event free survival (EFS)
SFOP (20)	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 4 PF only 23 PF + Brain or spine 20 Brain or spine only	5-year EFS 64.8% But 4% of patients were wrongly included: after review, 5-year EFS 71.8%
A 9961 (19)	379 A: 193 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 Regimen B: cisplatin, cyclophosphamide, and vincristine During radiotherapy, both regimens were treated with weekly vincristine	Multi-institutional study Randomized	0	73 (63 assessable patients) 32% PF only 40% Brain /Spine only 25% PF+ Brain /Spine	5-year EFS 81% A: 82% B: 80%
SJMB96 Gajjar (9)	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 1 PF + Brain or spine 9 Brain or spine alone	5-year EFS 83%
HIT-SIOP PNET 4 (21)	338 STRT: 169 HFRT: 169	STRT: 23.4 Gy to the CS axis and 54 Gy to WPF (42 days, 30 fractions of 1.8 Gy, 5 days per week) HFRT: 36 Gy to the CS axis and 60Gy 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: Vincristine during RT (maximum of 8 doses) plus 8 cycles of adjuvant chemotherapy (cisplatin, lomustine and vincristine)	Multi-institutional study Randomized.	1	0	5-year EFS 79% STRT: 78% HFRT: 81% EFS of children with all reference assessments and no large residual tumor was 82% ± 2% at 5 years.

Proton beam therapy is becoming increasingly used for patients with medulloblastoma to reduce 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 (22).

Presently there are two on-going major trials:
PNET 5 MB – Favourable risk patients are 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 are randomized in one of 2 arms: the aim is 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).

SJMB12 – The standard-risk group is divided in 3 strata determined by analysis of the tumour tissue for tumour biomarkers: WNT (Stratum W2 – positive for WNT biomarkers), 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 receive standard dose CSI with boost to the primary tumour site (23.4/54 Gy), followed by 4 cycles of maintenance chemotherapy (cisplatin, vincristine, cyclophosphamide). Some participants will complete aerobic training and/or neurocognitive remediation. In stratum S1, after completion of 4 cycles of chemotherapy, participants who are skeletally mature will receive maintenance chemotherapy with vismodegib.

1.3. Treatment of high risk medulloblastoma

Prior to the 1990s, outcome for HR-MB was poor, with 5-year EFS <50% (23–27). To improve survival, regimens looked to intensify treatment, either by increasing the dose of radiation, using high- dose chemotherapy and stem cell rescue or intensive chemotherapy regimens or using radiosensitisers. Since then, there have been several national or institutional trials that have achieved 5-year EFS rates of around 60% (summarised in Table 1) (9, 28–32). The approaches used are dependent on national or institutional trials experience and include (i) high-dose chemotherapy prior to (or occasionally post-) craniospinal RT (9, 28, 29) (ii) HART; twice daily (16, 29, 32) and (iii) conventional craniospinal RT (once daily), most commonly prior to maintenance chemotherapy.(30, 31)

Patient cohorts however are small and often selective. In addition, the criteria for risk stratification have varied over time and between studies. None considered biological stratification or subgroup analysis. The relative merits of these approaches 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.

Study	Number of Patients	Radiotherapy dose	Definition of High Risk	Chemotherapy	Comments	Toxic Deaths	Progression on treatment	Event free survival (EFS)
SJMB96 (9)	48: M0 = 6; M1 = 9; M2 = 6; M3= 27	36 – 39.6 Gy	Residuum >1.5cm2 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 Quality of survival data published	0	1	5-year EFS 70%
HART (UK) (16)	34: M1 = 9; M2 = 3; M3= 24	1.24 Gy fractions bd to 39.68 Gy	Only M+ patients	Vincristine with radiation 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 (30)	161 Centrally reviewed: M0 = 5; M1 = 18; M2 = 10; M3= 49	36 Gy	Residuum >1.5cm3, M+ and supratentorial PNET (all stages)	Carboplatin and vincristine during radiation 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 M1 = 77% M2 = 50% M3 = 67%
POG 9031 (31)	224: M1 = 29; M2 = 36; M3= 34; M4 = 9	35.2 – 40.0 Gy	T3b/T4 at the time of surgery (72), M+ (108) or residuum >1.5cm3 (44).	Randomised 3 x cisplatin and etoposide before or after radiation Maintenance with 7 x cyclophosphamide and vincristine	72 were Chang Stage T3b/T4, M0, no residual. No quality of survival data published	None reported	12 in the CT 1st arm	5-year EFS 66% CT 1st 70% RT 1st
Milan (29)	33: M1 = 9; M2 = 6; M3= 17; M4 = 1	HART 31.2 – 39 Gy	Only M+ patients	10 weeks chemotherapy pre-radiation (methotrexate, vincristine, etoposide, cyclophosphamide, carboplatin) Post radiation 2 x HD chemotherapy (Thiotepa) or maintenance with 12 moths CCNU and vincristine	Limited centre study Subsequent neuro toxicity reported.	None reported	5 (pre-radiation) 2 (on maintenance therapy	5-year EFS 70%
Institut Gustave Roussy (France) (28)	24: M0 = 5; M1 = 0; M2 = 4; M3 = 15	18 Gy (1) 25 Gy (2) 36 Gy (19) 40 Gy (1) 54 Gy focal (1 sPNET)	Residuum > 1.5 cm2, M+ disease, MYCN amplification or supratentorial PNET (3)	2 x carboplatin and etoposide pre- radiation 2 x HD chemotherapy (Thiotepa) Maintenance with temozolamide	Single institute study Neurocognitive data reported	0	0	5-year EFS 65% 5-year EFS 72% in metastatic MB
HIT 2000 (Germany) (32)	123 M1 = 36 M2 / M3 = 87	HFRT 40 Gy	Only M+ patients	2 x cycles of pre-radiation chemotherapy (cyclophosphamide, vincristine, methotrexate, carboplatin, etoposide and intraventricular methotrexate) Maintenance with 4 cycles cisplatin, CCNU, vincristine	Well tolerated.	0	14 (pre-radiation) 1 (after radiation) 31 (during maintenance or at end of treatment)	5-year EFS 62%
PNET HR + 5 France (33)	51 M0 = 14 M1 =3 M2/3 = 34	36 Gy CSI Unless Residual disease alone then 23.4 Gy	Residuum > 1.5 cm2, M+ disease, MYCN/MYC amplification, LCA histology	Carboplatin/etoposide x 2 Thiotepa HD x 2 Temozolomide Maintenance x 6	French National Study			5 year EFS 76% 5 year OS 76%

Table 5: Summary of clinical studies undertaken in HR-MB. 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.

1.4 Residual Disease

Extent of resection is still currently considered of as a prognostic variable in medulloblastoma when overt metastatic disease is excluded by initial staging. Its influence on PFS and OS however is not clear. Apart from the CCG-921 trial, undertaken in the pre-magnetic resonance imaging (MRI) era, there are roughly an equal number of studies that identify, or not, an association between increased extent of resection and OS. In the biggest randomised trial so far reported for non-metastatic medulloblastoma patients by Packer et al in 2006, the 15 patients with post-operative residual disease did not have a significantly worse prognosis than the others. (19) 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 (9) The presence of residual post-operative disease was prognostic in the SIOP PNET 4 trial (21) 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. (34). 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. (35) 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.(36)

It is probable that the prognostic benefit of a total resection is attenuated after accounting for molecular subgroup affiliation.(3) Considering all these data it was felt that there is a paucity of supportive evidence that intensifying therapy to the craniospinal axis improves local control in the setting of subtotal resection.

It is recommended that residual tumour where second look surgery is not considered appropriate without any other high-risk factors should be treated as standard risk disease.

1.5. SHH/TP53

The patient group with SHH-activated medulloblastoma with *TP53* mutation also represents a small group within the medulloblastoma entity with an annual accrual rate of approximately 5-10 patients in Europe. This group has a very poor prognosis and there is currently no consensus on the treatment of SHH-activated, germline *TP53*-mutated medulloblastoma patients although those with somatic mutations are treated on high risk protocols. The loss of p53 function is thought to confer resistance to chemotherapy (37, 38), 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 (39). Alkylating drugs especially seem to exert a high geno-toxic stress in *TP53*-deficient backgrounds (40). In a historic cohort of n=37 patients with SHH-activated, germline *TP53*-mutated medulloblastoma treated with surgery, chemotherapy and radiotherapy, 3- and 5-year-EFS was 20% and 16% respectively, and no long-term survivors were detected (Milde, Pfister et al., unpublished). 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 TP53 germline patients is not yet clear although one option is to treat as per the SHH-TP53 arm of PNET 5 MB or to contact one of the clinical advisors listed in the title page of this document.

1.6. Treatment of Infant and young children Medulloblastoma.

1.6.1 Sonic Hedgehog infant medulloblastoma

SHH-MBs are characterized by pathogenic activation of SHH signaling. At this age, the majority belong to the TP53-wildtype. The nodular/desmoplastic histologic subtype is almost exclusively found in this molecular group, while the extensive nodularity subtype is less common. Results of retrospective and prospective studies suggest that infants with SHH-driven medulloblastoma show a more favourable clinical outcome than those with Group 3 or Group 4.(5) Intertumoral heterogeneity amongst SHH-MB subgroup tumors has been described in terms of molecular subtypes (α, β, γ, and δ) with distinctive patient demographics and genetic lesions, as well as, in some studies, clinical outcomes.(41) Infant SHH tumors are mainly distributed across SHHβ and SHHγ, with different copy-number profiles and outcomes. SHHβ tumors are frequently metastatic and have a worse overall survival compared with SHHγ. Moreover, SHHγ are enriched for the medulloblastoma with extensive nodularity (MBEN) histology, which is known to foretell a more indolent clinical behavior. (5, 16, 42, 43)

The nodular-desmoplastic subtype is associated with improved survival in infants. In this group of young patients, radiation therapy may be successfully omitted (44, 45). Radiation-sparing treatments involve systemic chemotherapy with intraventricular therapy (HIT-SKK'92 protocol) or high-dose chemotherapy with stem cell rescue (44, 47, 49) (CCG-99703 protocol) (46).

The best reported 5-year progression-free survival 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.(41) In the CCG-99703 trial, 5-year progression-free survival was 78.6% for patients with DN/MBEN who received conventional chemotherapy followed by repeated cycles of myeloablative chemotherapy. The incorporation of either autologous transplant such as in the Head Start studies and CCG99703 or intraventricular MTX is considered as the gold standard therapy or standard of care for SHH medulloblastoma (44, 45).

Studies ACNS1221 and SJYC07 omitting intraventricular MTX or high-dose chemotherapy with autologous stem cell support, performed post-hoc molecular profiling and revealed inferior outcomes across all SHH medulloblastoma, but most importantly inferior outcome within both SHHβ and SHHγ (47, 48)(19,20). More specifically, for the SHHγ subgroup both ACNS1221 and SJYC07 report survival below 70%, suggesting that even for this seemingly good performing subtype, intensification of therapy is required (44, 48).The propensity for local relapses, particularly for SHHγ, both ACNS1221 and SJYC07 suggest that additional measures for local control are required.

Study	Number of Patients	Induction Chemotherapy	Marrow-ablative chemotherapy	Radiotherapy	Comments	Toxic Deaths	Progression on treatment	Event free survival (EFS)
HIT-SKK'92	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	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	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 23.4Gy with boost up to 54.6GY in case of noncomplete remission after chemotherapy and age >18y 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	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	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	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	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	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>6y) 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%

Table 7: Summary of clinical studies undertaken non SHH infant medulloblastoma

1.6.2. Standard/ High Risk Infant and young children with Medulloblastoma

In contrast to the favourable prognosis of young children with DN/MBEN medulloblastoma belonging to the SHH molecular subgroup, the outcome of infants with classic medulloblastoma or large-cell anaplastic medulloblastoma remains poor. (45, 49)

Most of the studies for young children with medulloblastoma aimed to delay or avoid radiotherapy by either using 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.

Conventional chemotherapy has been used in the several clinical trials. 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 medulloblastoma had significant worse five-year progression-free survival and overall survival rates (34+/-10 % and 41+/-11 %), than twenty patients with desmoplastic medulloblastoma (85+/-8 % and 95+/-5 %), independent of presence or absence of metastasis or postoperative residual tumour. (50) 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 medulloblastoma and 5 large-cell anaplastic variants with a 5-year overall survival of 33.3% and 0.0% respectively. (51) In the HIT2000 trial, nineteen patients with DMB/MBEN had better EFS and OS rates (5-year rates, 95% +/-5% and 100% +/-0%, respectively) than did 23 patients with CMB (5-year rates, 30% +/-11% and 68% +/-10%, respectively). Since the confirmation of the poor survival rates and frequent local relapses of patients with non-DMB/non-MBEN, local radiotherapy was recommended for all children aged >18 months with CMB or LCA MB. (32) 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 overall survival for patients with desmoplastic/nodular tumour MB was 58% +/-8% and 79% +/-7% respectively and 23% +/-12% and 31% +/-16% for patients with non-desmoplastic/non-nodular MB. Among 29 patients with documented disease progression, primary site failure was a component of failure in seven out of 10 patients who progressed before radiotherapy. In contrast, failure outside the posterior fossa occurred in 15 of 19 patients who progressed after radiotherapy. (52) Thirty-four non-SHH MB patients were treated in the SJYC07 trial with risk-adapted treatment with of induction chemotherapy, consolidation with focal radiation (intermediate-risk) or chemotherapy (high-risk), and metronomic maintenance therapy. The 5-year EFS and OS were respectively 10.6% and 50.5%. (48)

Intensive chemotherapy with **high dose chemotherapy** and stem cell rescue consolidation has been used in several protocols. Twelve patients less than 3 years old with non-metastatic classic MB were treated on 'Head

Start' I and II studies, consisting 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. (53) 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-desmoplastic medulloblastoma were 50.5% +/-11.8% and 60.6 +/-11.6% respectively. (47) The 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 MB (n=52) and LCA MB (n=13) were included in the trial. The 5-year EFS and OS rates for patients with classic MB were 26.6+/-6% and 53+/-7% and for patients with 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/LCA MB patients was 21+/-5%. These findings suggest that high-dose chemotherapy by itself might be enough to provide a cure for young patients with classic/LCA MB. (45) Prospective assessment of therapy based on molecular sub-classification has not yet been formally evaluated within clinical trials. In addition, to date there are no randomised controlled trials definitively demonstrating the significant benefit of high dose chemotherapy in non-desmoplastic medulloblastoma.

It is noted that the majority of studies have been performed in small numbers of infants and young children and in order to produce meaningful results in the molecular era global studies will be necessary.

1.7 Late Effects.

Standard-of-care for MB consists of maximal resection surgery, followed by craniospinal irradiation (CSI) and chemotherapy (CT). This combination leads to long-term survival rates of 60-80% but with a high risk of debilitating long-term toxicity.

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 a number of 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 slow rate of cognitive development and educational attainment. (54)

Second malignant neoplasms (SMNs), is a major complication of treatment, particularly radiotherapy, given in childhood and include meningioma and glioblastoma. (55) Cavernomas are also seen and usually discovered on routine follow up MRI imaging.

Endocrine dysfunction includes Growth Hormone deficiency, the most frequent sequelae, followed by thyroid dysfunction, and disorders of puberty.(22) 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 as a result of platinum-based therapies and cochlear radiation.(56)

Both the survivor and providers need to be aware of the survivor's treatment history to prioritize 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.

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.

Table 8. Table of late effects which may be seen in children and young people treated for medulloblastoma (adapted from Parkes et al (57))

2. DIAGNOSTIC CRITERIA

2.1 Imaging

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

2.2 Histopathology

A histopathological diagnosis of medulloblastoma group of tumours should be ideally made by neuropathologists experienced in reporting paediatric brain tumours. This can be achieved in the context of central pathology review. If available whereby samples are assessed by HE and a CNS embryonal tumour immunohistochemical panel including synaptophysin, GFAP, INI1, YAP1, GAB1, LIN28A, beta catenin etc. Once the histological diagnosis of medulloblastoma (including histological subtype and molecular group prediction if appropriate) is confirmed, the molecular diagnostic panel is activated as soon as feasible.

Desmoplastic nodular 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 and relatively weaker synaptophysin expression. Medulloblastoma with extensive nodularity (MBEN) are histologically similar to desmoplastic nodular MB but with marked expansion of the reticulin free nodules which tend to be large, elongated and convoluted with arrangement of well differentiated neoplastic cells in a streaming and even linear pattern within abundant neuropil. DN-MB and MBEN 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.

The large cell/ anaplastic (LCA) medulloblastoma variant is defined by the presence of significant anaplasia and or large cell morphology (large monomorphic cells with in a relatively large proportion of cells (>50% of neoplastic cell population). The determination of significant anaplasia is based on subjective histological interpretation and is defined by a significant degree of nuclear enlargement, pleomorphism, nuclear moulding and wrapping of cells, significantly higher mitotic counts and widespread apoptosis.

2.3 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.

2.3.1 Molecular subgrouping

Diagnosis of the genetically defined medulloblastoma entities should be undertaken according to the current WHO classification. The current (2021) classification defines the following variants:

- WNT-activated
- SHH-activated/*TP53* wild-type
- SHH-activated/*TP53* mutant
- non-WNT/non-SHH-activated (encompassing Group3 and Group4)

Assignment to the molecular genetic subgroup should be based at least two independent validated methods. In addition to the definition of the genetically defined MB entity by IHC (section 2.2), 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 MB; see next sections). Methods which have been used in clinical diagnostics include Illumina 850K/EPIC DNA methylation array, MS-MIMIC MassArray assay and Nanostring technology.

In addition, further SHH subtypes (PMIDs: 32296180, 32779246) and non-WNT/non-SHH subtypes I-VIII (PMID: 31076851) may be optionally assigned as using molecular methods described above, however these do not currently influence patient management.

2.3.2 Assessment of specific genetic defects (MYC, MYCN, chromosome 6 status)

Specific genetic defects should be assessed by iFISH, array-based or other methods.

iFISH is the ‘gold standard’ method for detection of these defects 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.

200 nuclei should be counted and *MYC* or *MYCN* amplification-positive cases are determined as those with ≥5% of nuclei showing evidence of gene amplification (signals consistent with double minute or homogenously staining region formation, and test probe copy number ≥ 4 times copy number of the reference signal). See Ryan SL et al. *MYC* family amplification and clinical risk-factors interact to predict an extremely poor prognosis in childhood medulloblastoma. Acta Neuropathol. 2012. 123: 501-13.

For monosomy 6 status, 200 nuclei should be counted, and positive cases are determined as those with ≥50% of nuclei showing a single signal for both the p- and q-arm probes (i.e. 1:1).

Other methods (e.g. array-CGH, SNP array) may be used, but their use is only recommended following validation of their performance against iFISH.

2.3.3 Mutation analysis

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

2.3.3.1 Genes for analysis in tumour samples

Genes for analysis currently include:

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

TP53, SMO, PTCH1, SUFU (all essential), ELP1, GPR161 (both optional): 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 MB 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.

2.3.3.2 Evaluation of germline alterations

In all cases with SHH medulloblastomas or *CTNNB1*-wt WNT medulloblastomas, urgent 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 the human genetics department responsible for genetic counselling and testing. The presence in the germline can be tested, using DNA extracted from the matching patient blood sample.

2.3.3.3 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.

2.4 Cerebrospinal fluid (CSF)

CSF via a lumbar spinal tap should be collected and the presence of medulloblastoma cells looked for. 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 will need to be repeated at a minimum of 14 days post-surgery.

3. TREATMENT DETAILS

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 the early obstructive hydrocephalus.

As in other tumours arising in the posterior fossa, medulloblastomas are often associated with a degree of obstructive 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 (57). 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 papilledema, or transependymal oedema in the modified version (1 point) (57, 58) An additional point is given for suspected medulloblastoma, ependymoma or dorsally exophytic brainstem glioma. 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 ventriculostomy may need to be considered before resection. As in up to 70% of children hydrocephalus resolves after resection, pre-operative insertion of a ventriculoperitoneal shunt is not recommended. Children who develop hydrocephalus post-operatively however are likely to require a shunt; an early decision avoids delay to adjuvant therapy.

Surgical resection typically involves a posterior fossa craniotomy, with exposure of the tumour within the fourth ventricle either through a transvermian or telovelar approach. Once the anatomy of the tumour and its relationship to eloquent structures is defined, the mass is usually debulked using suction, diathermy and an ultrasonic tissue aspirator. Tumour adherent to the fourth ventricular floor is reduced as much as possible, taking care not to damage the surface of the brainstem. Most of these tumours are highly vascular, and early control of large arterial pedicles, which usually arise from distal cortical branches of the posterior inferior cerebellar arteries, 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 a European study involving 428 patients, univariate analysis showed that children with SHH tumours over 4.3 years of age had a better PFS when the residual tumour was less than 1.5 cm^2 (4). The largest of these analyses evaluated 787 patients from 35 centres and showed that PFS, but not OS, was superior for those children undergoing gross total resection compared to those where the residual tumour was more than 1.5cm^2; there was however no benefit for gross total resection compared to up to 1.5 cm^2 of residual tumour (59). Extent of resection was not relevant to PFS or OS for patients with WNT, SHH or Group 3 tumours. In patients with Group 4 tumours, gross total resection improved PFS compared to a residual of over 1.5 cm^2. The authors conclude that the evidence that higher extent of resection carries a prognostic advantage is attenuated after molecular subgroups are taken into account, and recommend that small residual tumour components should not be resected at the risk of causing neurological deficit (59).

Despite ongoing surgical progress, the neurological morbidity of fourth ventricular tumour resection remains high. 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 at 28% throughout the recruitment period (60) The rates of new post-operative cranial neuropathy and new ataxia and gait abnormalities were 18% and 12.6% respectively. These rates are similar to the preliminary reports of the Nordic Cerebellar Mutism Study, which evaluated 426 patients from 26 centres in 10 European countries. Surprisingly, both studies have 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 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. (61) Whether particular protection of this region will result in a reduced rate of mutism remains to be explored.

3.2 Radiotherapy

Radiotherapy is a fundamental element in the management of children with medulloblastoma and postoperative craniospinal radiotherapy (CSI) is considered as the cornerstone of curative treatment. 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 LR-MB to reduce long-term sequelae whereas the research approach in HR-MB is to improve clinical outcome 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.

The current standard treatment of MB includes initial surgery followed by a combination of craniospinal irradiation (CSI) and chemotherapy. Despite advances in systemic therapy and neurosurgical techniques, CSI remains the standard radiotherapy technique. Conventionally, children with MB are categorized post-operatively as standard-risk (66% of patients) or high-risk (34% of patients). Children aged less than 3 years are generally managed with a chemotherapy only approach.

Timing;

Aim 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)

Overview;

The CSI component of treatment is planned and administered in a relatively conventional manner; however, irradiation of the primary site boost after CSI is best delivered with conformal planning.

Target Volume Definitions

Craniospinal Irradiation (CSI): The CSI volume includes the entire subarachnoid volume with special attention given to include the cribriform plate and temporal fossae 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 will be 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.

DOSE

High risk Medulloblastoma

Craniospinal irradiation (CSI) dose will be 36Gy in 20 fractions. Tumour bed boost 18Gy in 10 fractions

Total dose to boost PTV will be 54Gy.

Sites of brain or spinal metastasis (M2 & M3) to boost also to 50.4Gy (if felt appropriate).

Standard risk Medulloblastoma

Craniospinal axis: Phase 1 23.4Gy in 13 fractions and phase 2; 30.6Gy in 17 fractions to boost tumour bed.

Total dose to boost PTV will be 54Gy.

Modifications due to Haematological Toxicity;

- Thrombocytopenia - Radiotherapy will continue uninterrupted for thrombocytopenia unless the patient suffers from a significant haemorrhage or platelet transfusion refractory thrombocytopenia. Patients developing thrombocytopenia below locally recommended transfusion thresholds, should be given transfusions of platelets to maintain the count above this level in order to prevent CNS haemorrhage and treatment continues as planned.

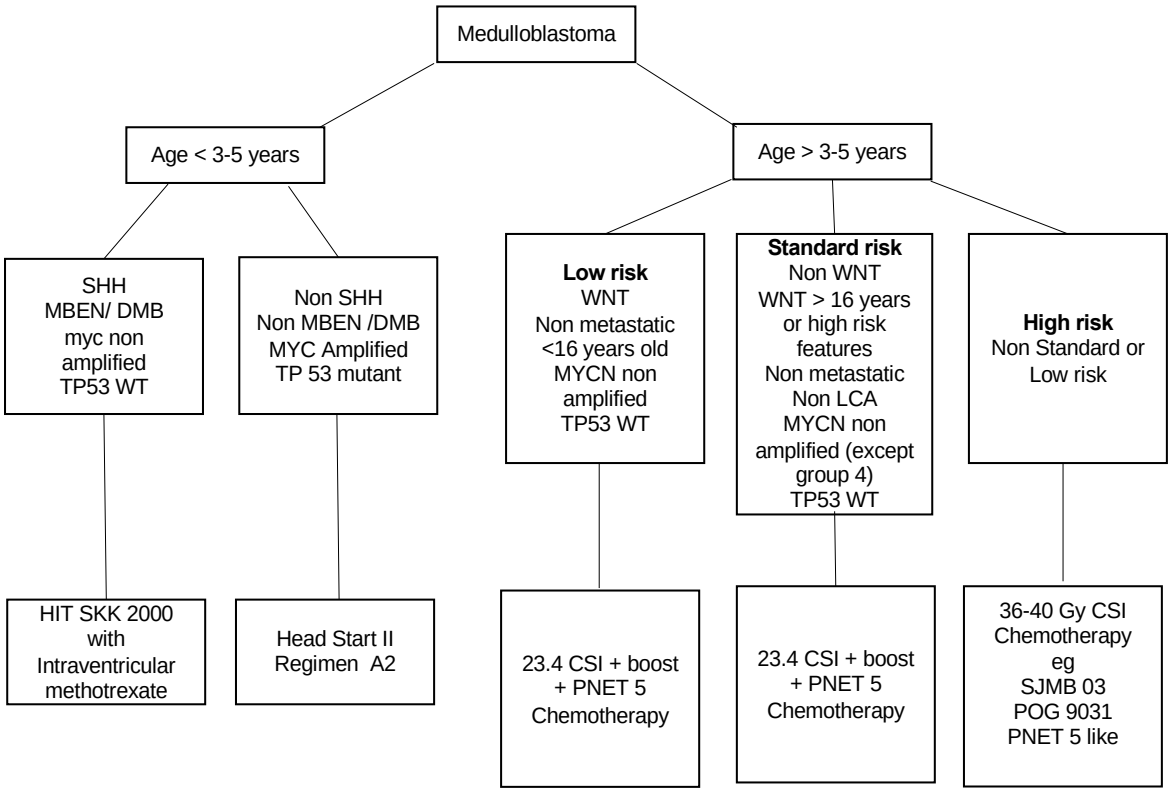
Neutropaenia - If a neutrophil count of $< 0.5 \times 10^9$ /L occurs, then G-CSF 5ug/kg (s.c. or i.v.) may be given daily to maintain a neutrophil count of $> 0.5 \times 10^9$ /L. If given, G-CSF should continue until the neutrophil count rises to $> 1.0 \times 10^9$ /L for two successive days.

Anaemia - The haemoglobin level should be maintained at a minimum level of 100 g/L during RT or according to national standards.

3.3 Chemotherapy Treatment recommendations.

Chemotherapy has been an essential part of the treatment of children with medulloblastoma for many years. There are a number of chemotherapeutic regimens which are generally recommended on the basis of age or risk factors. The following section outlines this in more detail.

Overall treatment schema for children with medulloblastoma.



Treatment recommendations for children older than 3-5 years old

	Molecular features	Histology	Residual	Metastatic disease	Treatment
Low Risk	WNT (< 16 years old) TP53 wild type, MYCN not amplified	Classic, Nodular Desmoplastic	<1.5cm2	M0	23.4 Gy + BABABABA
Standard Risk	No high risk biology ie MYC not amplified TP 53 WT	Classical/ND	<1.5cm2	M0	23.4 Gy + BABABABA
	Not high risk	Classical/ND	≥1.5cm2	M0	Pre-radiotherapy Carbo/etop 23.4 Gy + BABABABA
	WNT (non LR) Unless M+ > 16 years	Any	Any	Any	23.4 Gy + BABABABA
High Risk	TP53 mutant (Somatic) MYCN/MYC amplified	Any	Any	Any	36 – 40 Gy + SJMB or POG 9931 or BABABABA
	Any	Any	Any	M+	36 - 40 Gy+ SJMB or POG 9931 or BABABABA

Treatment recommendations for infants and young children with medulloblastoma.

	Molecular features	Histology	Residual	Metastatic disease	Treatment
Low Risk	SHH TP53 wild type MYCN not amplified	DM/MBEN	Any	Any	HIT SKK 2000
Standard Risk	Not high risk	Classical	<1.5cm2	M0	Head Start II Regimen A2
High Risk	SHH TP53 mutant MYCN amplified	DM/MBEN	Any	Any	
	Any	Classical	≥1.5cm2	Any	
	Any	Classical	<1.5cm2	M+	
	c-myc	Classical	Any	Any	
	Any	Anaplastic Large Cell	Any	Any	

ALGORITHM FOR TREATMENT OF LOW RISK INFANT MEDULLOBLASTOMA:

Low Risk iMB:

- **DN/MBEN**
- **No MYCN amplification**
- **TP53 wild type**
- **SHH**

Cycle 1: HIT SKK with intraventricular methotrexate (MTX)

CR/PR/SD

Cycle 2: HIT SKK with intraventricular MTX

CR/PR/SD

Discuss with Embryonal Tumour Group if Progressive disease at any cycle

Cycle 3: HIT SKK with intraventricular MTX

CR/PR/SD

Cycle 4: HIT SKK with no intraventricular MTX

CR/PR/SD

Cycle 5: HIT SKK with no intraventricular MTX

Residual tumour on neuraxial MRI

Complete Remission as Assessed by Neuraxial MRI

Observation as per institutional policy

Discuss with Embryonal Tumour Group

3.4 Infant – Low risk

TREATMENT GUIDANCE FOR LOW RISK INFANT MEDULLOBLASTOMA

Patients under 4 years of age with wild type TP53 and MYCN non–amplified histological DM/MBEN tumours will be treated with the HIT2000 strategy of systemic chemotherapy with intraventricular methotrexate, regardless of residual tumour or metastatic status. Patients with low risk iMB will receive 5 cycles of HIT SKK chemotherapy as per HIT2000. Systemic chemotherapy should commence within 28 days of surgery. Systemic chemotherapy should not be delayed to allow for the insertion of Ommaya/Rickham reservoir. Patients with residual tumour after 5 cycles of chemotherapy should be discussed with the Embryonal Tumour Group and should be re-evaluated for second look surgery.

Patients receive 5 cycles of systemic chemotherapy according to HIT 2000. The first 3 cycles contain systemic and intraventricular methotrexate. Intraventricular chemotherapy will be administered via an Ommaya/Rickham reservoir (see Appendices A and B)

SIOPE does not support the routine use of intrathecal methotrexate administered by lumbar puncture/port for the treatment of patients with infant medulloblastoma in this guideline.

The first 3 cycles of standard HIT SKK chemotherapy last 27 weeks and consists of four blocks of systemic therapy with intraventricular methotrexate:

Block A - Cyclophosphamide/vincristine with intraventricular methotrexate

Block B - Methotrexate/vincristine with intraventricular methotrexate

Block B - Methotrexate/vincristine with intraventricular methotrexate

Block C - Carboplatin/etoposide with intraventricular methotrexate

The final 2 cycles of **modified HIT SKK chemotherapy** last 10 weeks and consists of two blocks of systemic therapy without systemic or intraventricular methotrexate:

Block A - Cyclophosphamide/vincristine only

Block C - Carboplatin/etoposide only

Treatment Overview

Week	1	3	5	7	Reassessment
	Intraventricular Methotrexate is given week1-7				
Block	A + intraventricular	B + intraventricular	B + intraventricular	C + intraventricular	MRI Head and spine
Week	10	12	14	16	
	Intraventricular Methotrexate is given week1-7				
Block	A + intraventricular	B + intraventricular	B + intraventricular	C + intraventricular	MRI Head and spine
Week	19	21	23	25	
	Intraventricular Methotrexate is given week1-25				
Block	A +intraventricular	B + intraventricular	B + intraventricular	C + intraventricular	MRI Head and spine
Week	28	31	34	37	
	No intraventricular methotrexate in weeks 28-27				
Block	A	C	A	C	MRI Head and spine CSF cytology

Investigations required before each phase/cycle:

	Diagnosis	Post-operative	Cycle 1 (ABBC)	Cycle 2 (ABBC)	Cycle 3 (ABBC)	Cycle 4 (AC)	Cycle 5 (AC)
Physical examination	X	X	X	X	X	X	X
Biochemistry, haematology			X	X	X	X	X
GFR	X		X	X	X		X
CSF cytology	X		X	X	X		
MRI Head	X	X	X	X	X		
MRI spine	X		X	X	X		
Audiology	X		Pre-Carboplatin	Pre-Carboplatin	Pre-Carboplatin	Pre-Carboplatin	Pre-Carboplatin

Standard HIT SKK chemotherapy blocks consist of systemic chemotherapy with intraventricular methotrexate delivered via Ommaya/Rickham reservoir. Preventive measures must be established to **exclude the intraventricular application of any other drug** other than methotrexate in compliance with local intrathecal chemotherapy practice.

Supportive Care for Low Risk Medulloblastoma

Steroids for anti-emesis must be avoided (hydrocortisone replacement as required)

Anti-emetics as per local policy

PJP prophylaxis as per local policy

Fungal prophylaxis as per local policy

Blood product support as per local policy

Please note:

Intraventricular doses of methotrexate are not the same as single intrathecal methotrexate dose routinely given in treatment of leukaemia/lymphoma

All units must ensure there are robust mechanisms to prevent the administration of intraventricular methotrexate and systemic vincristine on the same day

Block A: Cyclophosphamide/vincristine with intraventricular methotrexate

Block A	Route	Dose	Day 1	Day 2	Day 3	Day 4	Day 5
Cyclophosphamide	IVI	800mg/m^2/day	x	x	x		
Vincristine **	IV	1.5 mg/m^2 (max. 2mg)					x
Methotrexate $^{++}$	Intraventricular	2mg	x	x	x	x	
For weeks 28 and 34: no intraventricular methotrexate is administered							
See below for age-based dose reductions:							

**Systemic vincristine and intraventricular methotrexate must be given in accordance with national intrathecal policies and local risk assessment

Investigations before commencing Block A course of chemotherapy

Physical	Clinically well **Ensure reservoir is working**
Haematology	ANC > 0.5 x 10^9/L or WBC > 2 x 10^9/L Platelet count > 80 x 10^9/L (unsupported)
Biochemistry	Normal renal function **Assess liver function tests only if jaundiced:** Transaminases <1.5 x upper limit normal Bilirubin < 30 µmol/L

Dose modification for age and/or toxicity in Block A

NB: Dose modifications for age are specific to HIT SKK approach and not as per usual UK CCLG recommendations

Age	**0 – 5 months:**	Cyclophosphamide and vincristine 66% of the m² dosage
		Methotrexate 1mg per intraventricular dose
	6 – 11 months:	Cyclophosphamide and vincristine 80% of the m² dosage
		Methotrexate 2mg per intraventricular dose (full dose)
	>12months	Methotrexate 2mg per intraventricular dose (full dose)
Haematological toxicity	**Before block:** ANC < 0.5 x 10^9/L WBC < 2 x 10^9/L Platelets < 80 x 10^9/L	Delay chemotherapy by a week
	Delay ≥ 2 weeks	G-CSF support prior to dose reduction
	In case of first episode of sepsis and: WCC <0.5 x 10^9/L ANC <0.05 x 10^9/L	Consider G-CSF support
	In case of second episode of sepsis and: WCC <0.5 x 10^9/L ANC <0.05 x 10^9/L	Omit day 3 Cyclophosphamide
Vincristine toxicity	**Seizures**	Hold 1 dose, then rechallenge at 50%.
	Severe foot drop, paresis or ileus	Hold dose(s): follow local policy to treat constipation (except enemas if neutropenic), if present. When symptoms abate, resume at 1mg/m²; escalate to full dose as tolerated
	Constipation (in absence of paresis or ileus)	Follow local policy to treat constipation but continue vincristine
	Hyperbilirubinaemia	Assess LFTs only if patient is jaundiced. Withhold vincristine if bilirubin >50µmol/L. Administer 50% of dose if total bilirubin 25 - 50. Do not alter dose for abnormal transaminases
	Jaw pain	Treat with analgesics; do not modify vincristine dose.
Haemorrhagic cystitis		Follow local policy

Suggested administration of Block A chemotherapy

Hydration and MESNA may be amended as per local policy.

Day/ Time	Drug	Dosage schedule	Comments
Day 1 T=0 hrs	**Mesna** **(pre-hydration)**	Pre-hydration with Mesna 120mg/m^2 IV infusion for 3 hours starting 3 hours before cyclophosphamide.	In Glucose 2.5%/Sodium chloride 0.45% containing Potassium Chloride 20mmol/L Running at 125ml/m^2/hr
Day 1 T=3 hrs	**Cyclophosphamide** **(systemic)**	800mg/m^2/day IV infusion over 1 hour	In 0.9% sodium chloride
Day 1 T=3 hrs	**Mesna** **(hydration)**	Mesna 960mg/m^2 IV infusion over 24 hours	In Glucose 2.5%/Sodium chloride 0.45% containing Potassium Chloride 20mmol/L Running at 125ml/m^2/hr
DAY 1	**Methotrexate** **(intraventricular)**	0 – 5 months: 1mg intraventricular >6 months: 2mg intraventricular	
Day 2 T=3 hrs	**Cyclophosphamide** **(systemic)**	800mg/m^2/day IV over one hour	In 0.9% sodium chloride
Day 2 T=3 hrs	**Mesna** **(post hydration)**	Mesna 960mg/m^2 IV over 24 hours	In Glucose 2.5%/Sodium chloride 0.45% containing Potassium Chloride 20mmol/L Running at 125ml/m^2/hr
DAY 2	**Methotrexate** **(intraventricular)**	0 – 5 months: 1mg intraventricular >6 months: 2mg intraventricular	
Day 3 T=3 hrs	**Cyclophosphamide** **(systemic)**	800mg/m^2/day IV over one hour	In 0.9% sodium chloride
Day 3 T=3 hrs	**Mesna** **(hydration)**	Mesna 520mg/m^2 IV over 13 hours To finish 12 hours after completion of last dose of Cyclophosphamide	In Glucose 2.5%/Sodium chloride 0.45% containing Potassium Chloride 20mmol/L Running at 125ml/m2/hr
DAY 3	**Methotrexate** **(intraventricular)**	0 – 5 months: 1mg intraventricular >6 months: 2mg intraventricular	
DAY 4	**Methotrexate** **(intraventricular)**	0 – 5 months: 1mg intraventricular >6 months: 2mg intraventricular	
Day 5	**Vincristine** **(systemic)**	1.5mg/m^2/day slow IV bolus	Maximum dose: 2mg

See dose modification table for age based dose reductions

Block B: High-dose methotrexate for Low Risk Medulloblastoma with intraventricular methotrexate

Block B	Route	Dose	Day 1	Day 2	Day 3	Day 4
Methotrexate	IVI	5g/m^2	x	Methotrexate level time points and Folinic acid rescue differ for Low risk and Standard/High risk HDMTX approaches		
Vincristine **	IV	1.5 mg/m2 (max. 2 mg)			x	
Methotrexate ++	Intraventricular	2mg	x	x		
See below for age based dose reductions: Please note these are not the usual CCLG age modifications						

**Systemic vincristine and intraventricular methotrexate must be given in accordance with national intrathecal policies and local risk assessment

Investigations before the course of Block B chemotherapy

Physical	Clinically well: Free of infection, diarrhoea and mucositis **Ensure reservoir is working**
Haematology	Platelets > 30 x 10^9/L (unsupported)
Biochemistry	Renal function must be within normal limits corrected for age GFR or estimated GFR >60 ml/min/1.73 m^2 ALT <5 x upper limit normal Bilirubin < 30 µmol/L

Dose Modifications for age and toxicity in Block B chemotherapy

Age	**0 – 5 months**	Vincristine 66% of the m² dosage
		Methotrexate intraventricular 1mg
	6 – 11 months	Vincristine 80% of the m² dosage
		Methotrexate intraventricular 2mg
	>12months	Full doses of systemic and intraventricular chemotherapy
GI toxicity	**Mucositis**	Delay HDMTX dose until mucositis resolved then give 100% dose.
	Diarrhoea	Delay HDMTX dose until diarrhoea resolved and then give 100% dose
General	**Infection**	Delay until infection resolved and then give 100% dose.
Haematology	**Platelets <30 x 10^9/L (unsupported)**	Delay until platelets >30 x 10^9/L (unsupported)
Vincristine toxicity	**Severe foot drop, paresis or ileus**	Hold dose(s): follow local policy to treat constipation (except enemas if neutropenic), if present. When symptoms abate, resume at 1mg/m²; escalate to full dose as tolerated
	Constipation (in absence of paresis or ileus)	Follow local policy to treat constipation but continue vincristine
	Hyperbilirubinaemia	Withhold vincristine if bilirubin >50µmol/L. Administer 50% of dose if total bilirubin 25 – 50. Do not alter dose for abnormal transaminases
	Jaw pain	Treat with analgesics; do not modify vincristine dose.
Seizures	**Vincristine**	Hold 1 dose, then re-challenge at 50%.
	Methotrexate	In case of seizures which may be attributable to HDMTX contact the Embryonal Tumour group
Renal toxicity	Creatinine > 1.5 x baseline or GFR creatinine clearance upper limit of normal (ULN) for age:	Delay until returns to normal.
	GFR < 60ml/min/1.73 m^2	Delay for 1 week and repeat GFR. If persists > 2 weeks: Follow local advice
Liver toxicity	If after HDMTX administration: Bilirubin > 1.5 upper limit of normal (ULN) for age ALT/AST > 5 x ULN but <20xULN	Delay until returns to normal. Re-check in 36-48 hours and give next HDMTX dose if transaminase levels are decreasing and bilirubin is normal. Contact Embryonal Tumour Group for further advice

Administration of Block B systemic chemotherapy

Hydration and administration of sodium bicarbonate may be amended as per local policy.

Day/ Time	Drug	Dosage schedule	Comments
Day 1 T = 0 hrs	**Pre-hydration**	Pre-hydration Start at least 6 hours before intravenous methotrexate.	Glucose 2.5%/Sodium chloride 0.45% containing Potassium Chloride 20mmol/L and Sodium Bicarbonate 50mmol/L Running at 125ml/m^2/hr Check urine pH>7, if not increase sodium bicarbonate as per local policy. Do not start until pH>7 and maintain pH. Ensure urine output of ≥400ml/m2 over 4 hrs BEFORE starting Methotrexate
Day 1 T = 6hrs	**Methotrexate (systemic)**	5 grams/m^2 IV infusion (total dose) split as follows: 10% (0.5g/m^2) given over 0.5hrs 90% (4.5g/m^2) given over 23.5hrs	In sodium chloride 0.9% Infusion **must** stop 24 hrs after starting infusion even if not complete.
Day 1 T = 6hrs	**Hydration**	Run at 125ml/m2/hr or as required	In Glucose 2.5%/Sodium chloride 0.45% containing Potassium Chloride 20mmol/L and Sodium Bicarbonate 50mmol/L
DAY 1	**Methotrexate (intraventricular)**	0 – 5 months: 1mg intraventricular >6 months: 2mg intraventricular	
Day 2 T=24 hrs	**Post hydration**	Continue hydration until rescued	In Glucose 2.5%/Sodium chloride 0.45% containing Potassium Chloride 20mmol/L and Sodium Bicarbonate 50mmol/L Running at 125ml/m^2/hr
Day 2 T = 42hrs	**Folinic acid**	15mg/m^2 IV 6 hourly starting 42 hours after the start of the IV methotrexate infusion	Minimum of 6 doses. See Folinic acid Rescue for further details.
DAY 2	**Methotrexate (intraventricular)**	0 – 5 months: 1mg intraventricular >6 months: 2mg intraventricular	
Day 3 T=48 hrs	**Post hydration**	Continue hydration until rescued	In Glucose 2.5%/Sodium chloride 0.45% containing Potassium Chloride 20mmol/L and Sodium Bicarbonate 50mmol/L Running at 125ml/m^2/hr
Day 3	**Vincristine**	1.5mg/m2/day slow IV bolus	Maximum dose: 2mg

See dose modification table for age based dose reductions

Folinic acid Rescue for Low Risk Infant Medulloblastoma:

Please note:

The original HIT SKK study mandates a minimum of 6 doses of folinic acid in Block B for neuroprotection – this is different from current leukaemia/lymphoma protocols
Folinic acid rescue must be continued until 72 hours after starting systemic methotrexate infusion
The timing of methotrexate levels and folinic acid is different in for patients with standard/high risk iMB

It is important to note that for this schedule the folinic acid rescue starts very late at 42 hours. **Therefore the initial folinic acid should be administered intravenously, so that the rescue is optimal.**

Methotrexate plasma concentrations are measured at hours 24, (36*), 42, 48 and 54 hours from start of the methotrexate infusion. The 36 hour level is only required if impaired methotrexate excretion is expected (see below).

If the serum concentration of Methotrexate **is below the expected levels** at 42, 48, and 54 hours after start of methotrexate infusion, further evaluations of Methotrexate serum levels are not necessary.

Folinic acid rescue has to be continued until 72 hours after start of methotrexate infusion.

Time from start of methotrexate	Routine creatinine measurement	Methotrexate concentration	Folinic acid dose (mg/m^2)
24 hours	yes	<150µmol/L	-
36 hours *		<3µmol/L	-
42 hours	yes	≤1µmol/L	15mg/m^2 intravenous
48 hours	yes	≤0.4µmol/L	15mg/m^2 iv
54 hours		≤0.25µmol/L	15mg/m^2 iv
60 hours **		**	15mg/m^2 iv/po
66 hours **		**	15mg/m^2 iv/po
72 hours **		**	15mg/m^2 iv/po

Please note:

*36 hour methotrexate level is required if impaired methotrexate excretion is expected

** Change to oral folinic acid can be considered after 60 hours

Block C: Carboplatin/etoposide with intraventricular methotrexate

Block C	Route	Dose	Day 1	Day 2	Day 3	Day 4	Day 5
Carboplatin *	IVI	200mg/m^2/day	□	□	□		
Etoposide *	IVI	150mg/m^2/day	□	□	□		
Methotrexate ++	Intraventricular	2mg	□	□	□	□	
For weeks 31 and 37: no intraventricular chemotherapy is given							
See below for age based dose reductions: Please note these are not the usual CCLG age modifications							

NB: *Systemic chemotherapy and intraventricular methotrexate must be given in accordance with national intrathecal policies and local risk assessment

Investigations before Block C course of chemotherapy

Physical	Clinically well **Ensure reservoir is working**
Haematology	ANC > 0.5 x 10^9/L or WBC > 2 x 10^9/L Platelet count > 80 x 10^9/L (unsupported)
Biochemistry	Normal renal function GFR >60 ml/min/1.73 m^2 (calculated using radio isotope) LFT <5 x upper limit normal Bilirubin < 30 µmol/L
Audiogram	Hearing loss <16dB at 1,000–3,000 Hz AND < 40 dB at 4,000–8,000 Hz

Dose modification

NB: Dose modifications for age are specific to HIT SKK approach and not as per usual UK CCLG recommendations

Age	**0 – 5 months**	Carboplatin 66% of the m² dosage
		Methotrexate intraventricular 1mg
	6 – 11 months	Carboplatin 80% of the m² dosage
		Methotrexate intraventricular 2mg
	>12months:	Methotrexate intraventricular 2mg
Carboplatin allergy	**Grade ≥2**	Replace with Cyclophosphamide 800 mg/m^2 per day
Haematological toxicity	**Before block:** ANC < 0.5 x 10^9/L WBC < 2 x 10^9/L Platelets < 80 x 10^9/L	Delay chemotherapy by a week until recovery
	After block: **In case of first episode of sepsis and: WCC <0.5** x 10^9/L ANC <0.05 x 10^9/L	Consider G-CSF post sepsis or slow WCC/Neutrophil recovery
	In case of second episode of sepsis and: WCC <0.5 x 10^9/L ANC <0.05 x 10^9/L	Omit day 3 Carboplatin and etoposide
Ototoxicity Note: dose modification is performed based on the highest grade of hearing loss, i.e. the "worst ear"	Hearing loss: 16–30 dB at 1,000–3,000Hz or > 40 dB at 4,000–8,000Hz	Reduce carboplatin to 125 mg/m²/day
	Hearing loss > 30 dB at 1,000–3,000 Hz	Replace carboplatin with cyclophosphamide 800 mg/m²/day
Nephrotoxicity	Creatinine > 1.5 x normal or GFR < 80 ml/min/1.73 m^2	Delay chemotherapy by 1 week. Proceed with 100% if renal function normalises
	GFR remains > 60 but < 80 ml/min/1.73 m^2 after 1 week	reduce Carboplatin to 125 mg/m^2/day
	GFR remains < 60 ml/min/1.73 m2 after 1 week	Replace Carboplatin with Cyclophosphamide 800 mg/m^2/day

Administration of Block C chemotherapy

Day/ Time	Drug	Dosage schedule	Comments
Day 1 T=0 hrs	**Carboplatin**	200mg/m^2 IV infusion over 1 hour	In Glucose 5%
Day 1 T=1 hrs	**Etoposide**	150mg/m^2 IV infusion over 4 hours	In Sodium Chloride 0.9% or Glucose 5% as per local policy
DAY 1	**Methotrexate (intraventricular)**	0 – 5 months: 1mg intraventricular >6 months: 2mg intraventricular	
Day 2 T=0 hrs	**Carboplatin**	200mg/m^2 IV infusion over 1 hour	In Glucose 5%
Day 2 T=1 hrs	**Etoposide**	150mg/m^2 IV infusion over 4 hours	In Sodium Chloride 0.9% or Glucose 5% as per local policy
DAY 2	**Methotrexate (intraventricular)**	0 – 5 months: 1mg intraventricular >6 months: 2mg intraventricular	
Day 3 T=0 hrs	**Carboplatin**	200mg/m^2 IV infusion over 1 hour	In Glucose 5%
Day 3 T=1 hrs	**Etoposide**	150mg/m^2 IV infusion over 4 hours	In Sodium Chloride 0.9% or Glucose 5% as per local policy
DAY 3	**Methotrexate (intraventricular)**	0 – 5 months: 1mg intraventricular >6 months: 2mg intraventricular	
DAY 4	**Methotrexate (intraventricular)**	0 – 5 months: 1mg intraventricular >6 months: 2mg intraventricular	

ALGORITHM FOR TREATMENT OF STANDARD/HIGH RISK INFANT MEDULLOBLASTOMA:

Standard and High Risk iMB:

- **Histology: non – DN/MBEN**
- Residual </>1.5cm^2
- M0-M3
- *MYCN/MYC* amplified/*TP53* mutant

HEAD START II: induction chemotherapy every 21-28 days

Reassessment after cycle 2

PD: discuss with Embryonal Tumour Group

SD/PR/CR

Reassessment after cycle 5

PD: discuss with Embryonal Tumour Group

Consider Stem cell collection after cycle 5

Complete Response:

High Dose Chemotherapy

Residual tumour:
Second look surgery
Consider high dose chemotherapy

Reassessment after high dose chemotherapy and stem cell rescue

Complete remission: consider Radiotherapy for patients with:

- LCA pathology
- Group 3 methylation subgroup
- Metastatic disease

Residual disease: discuss with Embryonal Tumour Group

3.5 TREATMENT GUIDANCE FOR STANDARD AND HIGH RISK iMB:

Patients with standard and high risk infant medulloblastoma will receive **5 cycles of intensive induction chemotherapy** in accordance with Head Start II Regimen A2 (Chi JCO 2004). Chemotherapy should aim to start within 28 days after surgery. The cycles should be given every 21-28 days.

Stem cell collection should be undertaken as per local policy. There is no particular guidance for stem cell collection off the back of induction chemotherapy. Cold harvest with GCSF prior to commencing induction chemotherapy or after 5th cycle of induction chemotherapy is acceptable. Child considered ineligible for stem cell collection should be discussed with the 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 will take place in patients who have not progressed during the induction phase of therapy.

Induction chemotherapy for High and Standard Risk Medulloblastoma - Cycles should be given every 21-28 days.

Drug	Dose	Route	1	2	3	4	5	6	7	8	15
Vincristine *	0.05 mg/kg (max 2mg)	IV	●							●	●
Cisplatin	3.5 mg/kg	IVI 6hr	●								
Cyclophosphamide	65 mg/kg	IVI 1hr		●	●						
Etoposide	4 mg/kg	IVI 2hr		●	●						
Methotrexate	400mg/kg (max 20g)	IVI 4hr				●					

***Cycles 1-3: vincristine in cycles 1,2 and 3 (total of 9 doses of vincristine). Cycle 4 and 5: no vincristine**

Expected Methotrexate concentrations (NB: this is different to the Low Risk iMB schedule)

Please note: these methotrexate concentration levels are not the usual CCLG levels. The lower levels of methotrexate (MTX) concentration are taken from the Head Start programme with the goal of reducing methotrexate-induced white matter changes.

Hour	MTX-serum concentration in µmol/l	Folinic acid-rescue
24	< 10	15mg/m^2 IV q6 hourly
48	< 1	15mg/m^2 IV q6 hourly
72	≤ 0.1	Stop rescue and hydration

If the serum MTX concentration is lower than target levels, as expected, folinic acid rescue should continue as below until MTX-serum concentration is ≤0.1µmol/l.

If the serum MTX concentration is not below the target levels as expected, folinic acid rescue should follow local guidance.

Start Granulocyte colony stimulating factor (GCSF) 5 micrograms/kg/day IV/SC from day 5 until count recovery.

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. Aggressive anti-emetics upfront are essential.

Care should be taken for patients that develop febrile neutropenia while being rescued from HD MTX. Avoid drugs that may interact with methotrexate and nephrotoxic drugs as per local guidance. Meropenem should be considered the antibiotic of first choice in management of febrile neutropenia during high dose methotrexate administration.

Irradiated blood products as per institutional policy

PJP prophylaxis as per local policy

Fungal prophylaxis as per local policy

Blood product support as per local policy

Investigations required before each phase/cycle

	Diagnosis	Post-op	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Prior to HDC
Physical examination	X	X	X	X	X	X	X	X
Biochemistry, haematology *			X	X	X	X	X	X
GFR			X		X		X	X
CSF cytology*		X			X			X
MRI Head	X	X			X			X
MRI spine	X				X			X
Audiology			X	X	X	X	X	X
Stem cell collection		***						X
Echocardiogram								X
Pulmonary assessment								X

***Blood tests: renal function, bicarbonate, Ca, Mg, Phosphate, LFT, tubular resorption phosphate, FBC**

**** If CSF abnormal at diagnosis, repeat LP after alternate courses of chemotherapy and prior to high chemotherapy**

***** consider stem cell collection prior to cycle 1 chemotherapy**

Investigations prior to starting each cycle of induction chemotherapy

Physical	Clinically well **No evidence of active infection**
Haematology	ANC > 1 x 10^9/L and WBC > 2 x 10^9/L Platelets > 100 x 10^9/L (unsupported)
Biochemistry	Normal renal function GFR/eGFR >80 ml/min/1.73 m^2 Transaminases <1.5 x upper limit normal Bilirubin < 30 µmol/L
Audiogram	<16–30 dB at 1,000–3,000Hz and/or <40 dB at 4,000–8,000Hz

Administration of induction chemotherapy for standard and high risk infant Medulloblastoma Hydration and Mannitol may be altered as per local policy

Day	Lumen 1	Lumen 2	Notes
Day 1 T=0hr		Glucose 2.5% Sodium Chloride 0.45% containing 20mmol Potassium/L at 200ml/m2/hr for 3 hours	
Day 1 T=3hr	**Vincristine** 0.05mg/kg (max 2mg) IV Slow Bolus **Cisplatin** 3.5mg/kg IV Infusion in Sodium Chloride 0.9% for 6 hours	Glucose 2.5% Sodium Chloride 0.45% containing Potassium Chloride 20mmol/L and 60mL/L Mannitol 20% for 6 hours **Total hydration rate including cisplatin: 125ml/m^2/hr**	**No vincristine in cycles 4 and 5** Diuresis: If at any time the urine output falls below 3 ml/kg/hr for 2 hours give Mannitol 0.5g/kg (2.5ml/kg mannitol 20%) over 15-30 minutes. Avoid Furosemide.
Day 1 T=9hr		Glucose 2.5% Sodium Chloride 0.45% containing Potassium Chloride 20mmol/L and 60mL/L Mannitol 20% for 6 hours at 125ml/m^2/hr	
Day 1 T=15hr		Glucose 2.5% Sodium Chloride 0.45% containing Potassium Chloride 20mmol/L, Magnesium Sulphate 10mmol/L, Calcium Chloride 0.6mmol/L for 12 hours at 125ml/m^2/hr	
Day 2 T=3hr	**Etoposide** 4mg/kg IV Infusion in Sodium Chloride 0.9% for 2 hours	Glucose 2.5% Sodium Chloride 0.45% containing Potassium Chloride 20mmol/L and 78mg/kg Mesna for 24 hours at 125ml/m^2/hr	*****Monitor fluid balance. Reduce rate of infusion so hydration rate plus drugs provide at least 125ml/m^2/hr*** ***Dipstick urine for signs haematuria***
Day 2 T=5hr	**Cyclophosphamide** 65mg/kg IV Infusion in Sodium Chloride 0.9% for 1 hour		
Day 3 T=3hr	**Etoposide** 4mg/kg IV Infusion in Sodium Chloride 0.9% for 2 hours	Glucose 2.5% Sodium Chloride 0.45% containing Potassium Chloride 20mmol/L and 78mg/kg Mesna for 24 hours at 125ml/m^2/hr	
Day 3 T=5hr	**Cyclophosphamide** 65mg/kg IV Infusion in Sodium Chloride 0.9% for 1 hour		
Day 4 T=3hr		Glucose 2.5%/Sodium chloride 0.45% containing Potassium Chloride 20mmol/L and Sodium Bicarbonate 50mmol/L at 125ml/m^2/hr	
Day 4 T=7hr*	**High Dose Methotrexate** 400mg/kg IV Infusion in Sodium Chloride 0.9% for 4 hours	**Continue hydration until Folinic acid rescue complete**	
Day 5		**Folinic acid** 15mg/m^2 IV 6 hourly starting 24 hours after the start of the IV methotrexate infusion	
	Start GCSF 5 micrograms/kg/day IV/SC		Start GCSF after methotrexate rescue completed
Day 8	**Vincristine** 0.05mg/kg (max 2mg) IV Slow Bolus		**No vincristine in cycles 4 and 5**
Day 15	**Vincristine** 0.05mg/kg (max 2mg) IV Slow Bolus		

Dose modification for toxicity during induction chemotherapy

Age	**There is no dose alteration for age**	
Haematological toxicity	**Before block:** ANC < 1x 10^9/L WBC < 2 x 10^9/L Platelets < 100 x 10^9/L	Delay cycle by 1 week No dose modifications in subsequent cycles made for infections or delayed recovery. GCSF support.
Vincristine toxicity	**Seizures**	Hold 1 dose, then re-institute at 0.03mg/kg. If seizures do not recur, then escalate to full dosage
	Severe foot drop, paresis or ileus	Grades 3 or 4 neurotoxicity: Hold 1 dose of vincristine, then resume at 0.03mg/kg and escalate to full dosage when symptoms resolve.
	Hyperbilirubinaemia	Assess LFTs only if patient is jaundiced. Bilirubin >50mmol: hold next dose Bilirubin 25 – 49mmol/l: administer 0.03mg/kg, escalate to full dose if bilirubin falls below 25mmol/l
	Jaw pain	Treat with analgesics; do not modify vincristine dose.
	Constipation (in absence of ileus)	Follow local policy to treat constipation but continue vincristine
Renal toxicity	Creatinine > 1.5 x normal OR GFR <80 ml/min/1.73 m^2	Delay chemotherapy by 1 week, repeat creatinine and/or GFR. Proceed if normalises
	GFR 60 - 80 ml/min/1.73 m^2	Replace cisplatin with carboplatin 12mg/kg
	GFR <60 ml/min/1.73 m^2	Omit all platinum chemotherapy Consider 25% dose reduction of etoposide and cyclophosphamide
Ototoxicity Note: dose modification is performed based on the highest grade of hearing loss, i.e. the "worst ear"	Hearing loss: 16–30 dB at 1,000–3,000Hz or > 40 dB at 4,000–8,000Hz	Replace cisplatin with carboplatin 12mg/kg
	Hearing loss > 30 dB at 1,000– 3,000 Hz	Withhold platinums
Liver toxicity	Not MTX induced	Delay one week. Give if ALT < 10 x ULN and normal bilirubin
	Probable MTX induced i.e. up to 3 weeks after MTX	It is expected that patients receiving high dose Methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to two weeks following the methotrexate infusion and will not be considered toxicity requiring discontinuation of the drug
	Post – methotrexate: ALT > 20 x ULN for > 2 weeks	Consider additional aetiology. Discuss with Embryonal Tumour Group prior to next chemotherapy
	Bilirubin > 1.25 x ULN	Discuss with Embryonal Tumour Group if hyperbilirubinemia persists for longer than three weeks

Autologous stem cell collection

This should be undertaken as per local guidance for stem cell collection in accordance with JACIE regulations

Peripheral stem cells collection should be considered in steady state harvest prior to commencing chemotherapy or on recovery from 5th cycle of chemotherapy

Use G-CSF 10 micrograms/kg/day subcutaneously to prime bone marrow for stem cell collection

Irradiated blood products as per institutional policy

Target >6 x 10^6 CD34+ cells/kg should be collected and stored in at least 2 aliquots (3x10^6 CD34+ cells/kg) as per local policy

High dose chemotherapy (HDC) with autologous stem cell rescue (ASCR)

Treatment outline

Following completion of induction chemotherapy, if there is radiographic evidence of residual tumour on disease evaluation second-look surgery (SLS) should be considered. Second opinion from national neurosurgical leads should be sought. 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

Timeline for HDC and ASCR:

	Route	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5
Hydration	**IV**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**				
Carboplatin	**IV**	**X**	**X**	**X**											
Etoposide	**IV**				**X**	**X**	**X**								
Thiotepa	**IV**				**X**	**X**	**X**								
Stem cells	**IV**									**X**					
GCSF	**sc/IV**														**X**

Investigations before the course of High Dose Chemotherapy (HDC)

Physical examination	Clinically well Dental assessment
Tumour assessment	No evidence of progressive disease on MRI and CSF cytological assessment
Cardiology assessment	Normal echocardiogram FS >29% No evidence of pulmonary hypertension
Respiratory assessment	Normal chest x-ray and oxygen saturations Lung functions, if old enough and possible
Haematology	ANC > 0.8 x 10^9/L and unsupported platelet count > 80 x 10^9/L
Liver assessment	Normal liver function defined as < 1.5 x upper limit of normal and bilirubin < 30 µmol/L
Renal assessment	GFR >60 ml/min/1.73m^2 No significant tubulopathy
Audiology	If significant deafness consider discussion with Embryonal Tumour Group
Concomitant medications	Review concomitant nephrotoxic drugs

Administration of High Dose Chemotherapy

Day/Time	Drug
Day -8 T = -3 hrs	**Hydration** 125ml/m^2/hr for 3 hours Sodium chloride 0.9% or as per local practice Continue hydration until at least 24 hours post-stem cell infusion (or as per local policy)
Day -8 T = 0 hrs	**Carboplatin (see dose below)**
Day -7 T = 0 hrs	**Carboplatin**
Day -6 T = 0 hrs	**Carboplatin**
Day -5 T = 0 hrs	**Thiotepa (see dose below)**
Day -5 T = 3 hrs	**Etoposide (see dose below)**
Day -4 T = 0 hrs	**Thiotepa**
Day -4 T = 3 hrs	**Etoposide**
Day -3 T = 0 hrs	**Thiotepa**
Day -3 T = 3 hrs	**Etoposide**
Day 0	Autologous **stem cells** Infuse as per local policy
Day +5	GCSF 5mcg/kg/day SC/IV as per local policy until neutrophils greater than 1x10^9/L for 2 consecutive days or as per institutional policy

Drug	Dose	Administration
Carboplatin	AUC 7 mg/ml/min using Newell or Calvert formulae (as per local policy) or 16.6 mg/kg. Use lower of the two calculated doses and maximum dose of 500 mg/m^2	IV infusion over 4 hours on Day -8 to Day -6
Thiotepa	300 mg/m^2 or 10 mg/kg Use lower of the two calculated doses	IV infusion over 3 hours on Day -5 to Day -3
Etoposide	250 mg/m^2 or 8.3 mg/kg Use lower of the two calculated doses	IV infusion over 4 hours on Day -5 to Day -3

Dose modification of high dose chemotherapy conditioning for toxicity

Carboplatin allergy	Grade ≥2	Discuss with Embryonal Tumour Group
Haematological toxicity	**Before HDC:** ANC < 0.8 x 10^9/L Platelets < 80 x 10^9/L	Delay chemotherapy until count recovery
Ototoxicity Note: dose modification is performed based on the highest grade of hearing loss, i.e. the "worst ear"	Hearing loss: 16–30 dB at 1,000–3,000Hz or > 40 dB at 4,000–8,000Hz	Discuss with Embryonal Tumour Group and consider reducing Carboplatin to AUC 5.3mg/ml/min IV over 4 hours
	Hearing loss > 30 dB at 1,000–3,000 Hz	
Nephrotoxicity	GFR <60ml/min/1.73m^2	Delay start of chemotherapy by 1 week and recheck
	GFR 60-80ml/min/1.73m^2	Discuss with Embryonal Tumour Group and consider reducing Carboplatin to AUC 5.3mg/ml/min IV over 4 hours
	GFR remains < 60 ml/min/1.73m^2 after 1 week	Discuss with Embryonal Tumour Group
Liver toxicity	Transaminases > 1.5xULN	Delay chemotherapy until recovery
	Bilirubin > 1.5x ULN	Delay chemotherapy until recovery

Supportive care for High Chemotherapy and autologous stem cell rescue

Patients must not receive corticosteroids concomitant with chemotherapy administration for the sole purposes of anti-emesis.

Review concomitant nephrotoxic medications during conditioning

Co-trimoxazole as per local policy

Use irradiated blood products as per local policy

Antifungal prophylaxis as per local policy

Antiviral prophylaxis as per local policy

Skin care as per local policy for thiotepa

3.6 Treatment of Low/Standard Risk medulloblastoma.

Radiotherapy - see section 3.2

Chemotherapy

Regimen A Chemotherapy for Regimen A consists of cisplatin, CCNU and vincristine, at the following doses:

Cisplatin: 70 mg/m^2 IV (6 hour infusion) - day 1

CCNU (Lomustine): 75 mg/m^2 orally - day 1 (Whenever possible patients should be encouraged to swallow the capsules whole, without chewing or crushing. If this is not possible capsules may be opened and the content administered according to institutional guidelines.)

Vincristine (VCR): 1.5 mg/m^2 IV (maximum dose 2 mg) - day 1, 8 and 15 (VCR may be given as a bolus or short infusion as necessary to comply with local or national guidelines). N.B. Vincristine must be administered by IV routes only.

It is appreciated that different national groups and individual centres have varying but well-established methods of administering cisplatin.

Cisplatin to be given as an infusion over 6 hours

Hyperhydration to be used to maintain an adequate urine output

The use of mannitol to enhance urine output

The addition of calcium, magnesium and potassium to hydration fluids

The use of effective anti-emetics.

Careful monitoring of urine output with appropriate guidelines for treatment of insufficient urine output

Administration of carboplatin (if indicated as a substitute for cisplatin during maintenance chemotherapy)

Carboplatin 400 mg/m^2 IV is to be given as a 1-hour infusion.
Pre- and post-chemotherapy fluids should be administered in accordance with institutional practice.

The first cycle of maintenance chemotherapy must be started between 6 weeks and a maximum of 12 weeks after completion of radiotherapy, once the patient has count recovered to the following criteria:

The following haematological criteria must be met prior to commencement of each cycle:

ANC ≥ 0.5 x 10^9/L or leukocytes ≥ 2.0 x 10^9/L

Platelets ≥ 100 x 10^9/L

If count recovery does not occur within 12 weeks from completion of radiotherapy, please contact the Clinical Coordinators to discuss further treatment. Refer to section 14.2.1 for dose modifications

12.2.2 Administration of Chemotherapy–Regimen B

Chemotherapy for Regimen B consists of cyclophosphamide and vincristine at the following doses:

Cyclophosphamide: 1000 mg/m^2/d given as IV infusion, over one hour, once daily, day 1 and 2

Vincristine: 1.5 mg/m^2 IV (max. dose 2 mg) - day 1 (VCR may be given as a bolus or short infusion as necessary to comply with local or national guidelines.) N.B. Vincristine must be administered by IV routes only.

MESNA: The use of MESNA should be in accordance with institutional practice to reduce the risk of urothelial toxicity. If gross haematuria occurs on Day 1, MESNA should be increased in the first instance, if previously administered, or added if not previously given. Cyclophosphamide may be omitted on day 2 at the discretion of the treating Investigator. In the following course MESNA should be given in a dose of at least 120% of the dose of cyclophosphamide with hyper-hydration. The dose of cyclophosphamide may be halved (500 mg/m^2) on both days 1 & 2 if this is considered necessary. If well tolerated the standard dose should be administered in subsequent courses with MESNA and hyper- hydration.

Recommendation: MESNA 250 mg/m^2 IV before first cyclophosphamide infusion, 750 mg/m^2/24 hour, day 1-2.

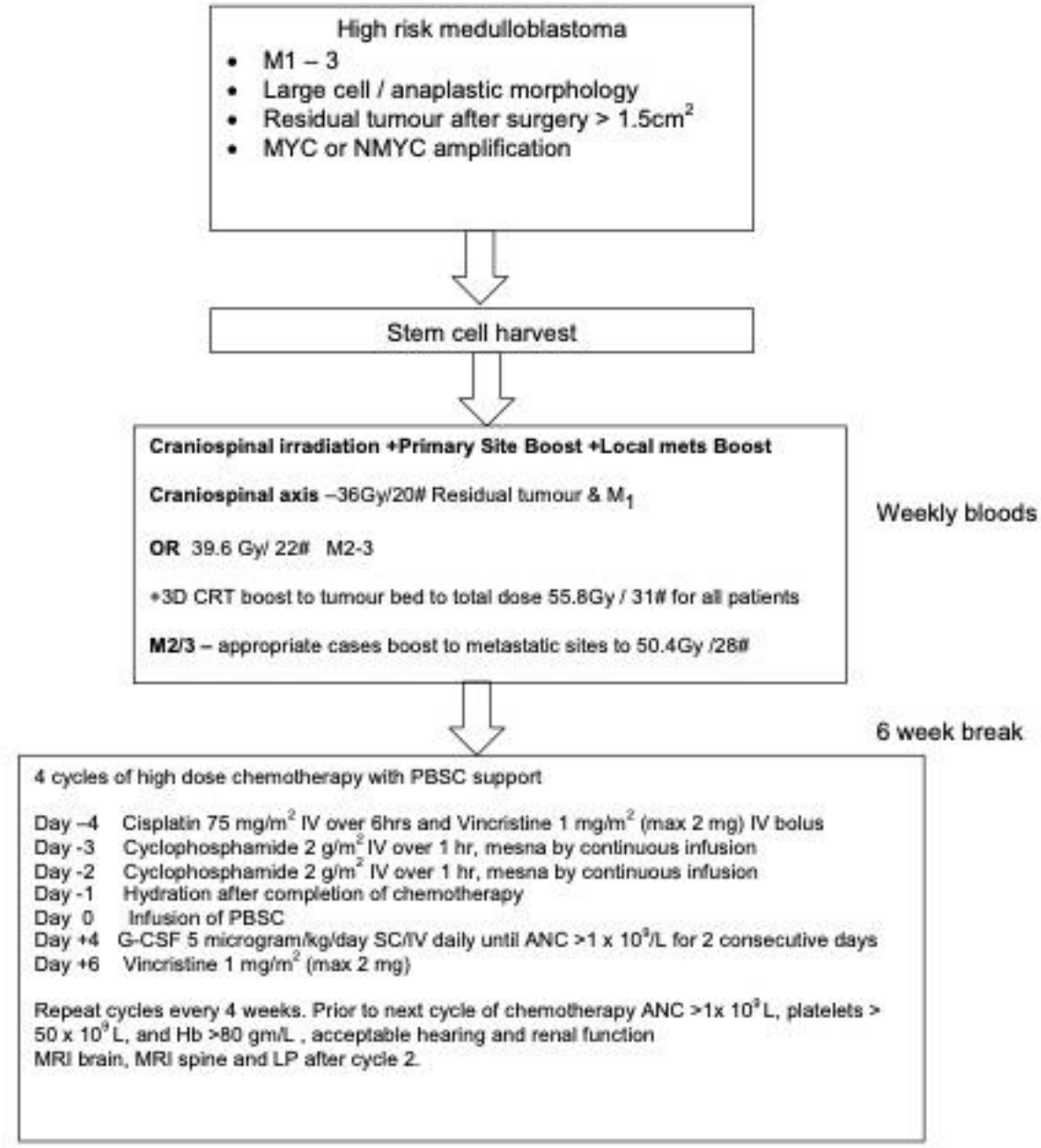
The following haematological criteria must be met prior to commencement of each cycle:

ANC ≥ 0.5 x 10^9/L or leukocytes ≥ 2.0 x 10^9/L

Platelets ≥ 100 x 10^9/L

HIGH RISK MEDULLOBLASTOMA.

High Risk SJMB



Summary flow sheet for chemotherapy

Cisplatin 75mg/m²	■									
Vincristine 1 mg/m²(max 2mg)	■									■
Cyclophosphamide 2g/m² over 1hr +mesna hydration		■	■							
PBSC					■					
GCSF 5mcg/kg/day (Continue until count recovery)									■	■	■
Day	**-4**	**-3**	**-2**	**-1**	**0**	**+1**	**+2**	**+3**	**+4**	**+5**	**+6**
Cycle 1											
Cycle 2											
Cycle 3											
Cycle 4											

Double lumen central line required for chemotherapy administration

Commence the first cycle of HD chemotherapy with stem cell support 6 weeks after completion of radiotherapy.

ANC is ≥1 x 10^9/L

Unsupported platelet count ≥50^9 x 10 /L

Hb 8 gm/dL $_2$ Normal renal function as defined by a corrected GFR ≥ 80 mL/min/1.73 m . Normal liver function as defined by an ALT concentration < 5 x the normal concentration and a bilirubin concentration <30 µmol/L

Repeat high dose cisplatin/cyclophosphamide/vincristine cycle three times at four weekly intervals but no sooner than:

ANC is ≥1 x 10^9/L (no G-CSF for 48 hrs)

Unsupported platelet count ≥50 x 10^9/L

Normal blood biochemistry – electrolytes, creatinine, urea, ALT, AST, Alkaline phosphatase, bilirubin,

albumin, magnesium, calcium, phosphate.
Prior to cycle 3 perform estimation of GFR by clearance of radioisotope and echocardiogram with measurement of fractional shortening.

Drugs
Vincristine 1mg/m2 (max dose 2 mg) IV bolus pre Cisplatin on Day -4 and repeated on

Day + 6
Cisplatin 75 mg/ m^2 IV over 6 hrs Day -4 with hydration

Cyclophosphamide 2 g/m2 IV over one hour on Day – 3 and -2 with hydration and mesna.

Mesna 2400mg/m^2/24 hours starting 3 hours prior to the first cyclophosphamide dose and continuing until 24 hours after the start of the last cyclophosphamide dose.

Dose Modifications and delays

SJMB 03.

1) Vincristine Toxicity

a. Seizures: Omit one dose, then consider reinstituting at 0.5mg/m^2 (1mg maximum) while anticonvulsants are continued. If seizures do not recur, return to full dosage at the time of next scheduled dose.
b. Neurotoxicity(grade3/4, footdrop, severeparesis, disablingparesthesias)or ileus. Omit one dose, resume vincristine at 0.5 mg/m^2 (1 mg maximum), and then return to full dosage when symptoms resolve.
c. Jaw Pain: Treat with analgesics (NOT salicylates or NSAIDS). Do not omit or reduce vincristine.
d. Hepatotoxicity:If total bilirubin is >30µmol/L, omit vincristine dose.If total bilirubin is 25-30 µmol/L, administer vincristine at 0.5 mg/m^2.

2) Cisplatin Toxicity a. Ototoxicity.
Grading for Audiometry is based on loss in both ears. Thus the grading (including that for modification of chemotherapy) is based on the Highest Grading i.e. the worst ear.
The Dose Modification of cisplatin is as follows: Hearing –Dose Modification:
< 16 dB at 1000-3000 Hz or ≤ 40 dB at 4000-8000 Hz
16-30 dB at 1000-3000 Hz or 40 dB at 4000-8000 Hz
>30 dB at 1000-3000 Hz
None
Substitute Carboplatin AUC 5.3 (see section b.
nephrotoxicity) for Cisplatin Omit any platinum
b. Nephrotoxicity:
Isotope GFR>60and<80ml/minper1.73m UsecarboplatinAUC5.3 instead of cisplatin for next cycle.
Using ^{51}Cr-EDTA clearance for determination of GFR, the dose of carboplatin is

calculated from the **51Cr-EDTA half-life (t1⁄2) value and patient's body weight**

Isotope GFR < 60 ml/min per 1.73m^2 omit any platinum for next course.
Perform estimation of GFR by clearance of radioisotope before next cycle

3) Cyclophosphamide

a. Haematopoietic toxicity: Delay cyclophosphamide until the ANC is≥1x10/L and platelet count ≥50 x 10^9/L. G-CSF may be used until 48 hrs prior to the next cycle of chemotherapy to get adequate ANC.

b. Haemorrhagic cystitis: The patient should be taken off treatment if patient has a Grade 4 toxicity.

Supportive care drugs

It is suggested that patients receive the following as per local policy:
Aciclovir or valaciclovir prophylaxis PCP prophylaxis
Antifungal prophylaxis

Suggested Monitoring

1) MRI scans of brain and spine

1. Pre-surgery including spine

Within 48hours of surgery
Post radiotherapy – pre chemotherapy

4. After two cycles of chemotherapy

e. Post treatment as per your institutional guidance

2) Audiometry

a. Prior to chemotherapy
b. After each cycle of chemotherapy
c. At the end of treatment
d. Follow up as per institutional guidance.

3) Renal functioning

a. Glomerular filtration testing using CrEDTA or test as approved by your institution. This should be done prior to the first cycle of chemotherapy, after 2 cycles and after completion of treatment. Additional measurement can be performed before cycles 2 and 4 at the treating clinician's discretion if there have been concerns about renal function.

4) Echocardiogram including measurement of fractional prior to first and after 3 cycle and after completion of treatment

High Risk POG 9031

For those choosing to use the POG 9031 protocol (31) initial chemotherapy should ideally be started within 3 weeks of surgery as per the outline below. Induction chemotherapy is followed by radiotherapy and following this 7 courses of vincristine and cyclophosphamide consolidation.

Induction consists of cisplatin 90mg/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 1000mg m^2 on day 1 and 2 and vincristine 2.0 mg/m^2 on day 1 (maximum dose 2.0 mg)

DAY	TIME	CHEMOTHERAPY
DAY 1	**T=0**	Pre-hydration Dextrose 5%/ Sodium Chloride 0.45% Total Volume 600mL/m^2 over 3 hours (max 900mL)
	T=3	Cisplatin **90mg/m^2** in Sodium Chloride 0.9% over 6 hours Hydration to run with Cisplatin and for 6 hours after Dextrose 2.5%/Sodium chloride 0.45% Potassium chloride 20mmol/1000mL Total Volume: 1320mL/m^2 over 12 hours (Maximum volume 1980mL)
	T=15	Mannitol 10% 180mL/m^2 over 12 hours (max 270mL)
		Post Hydration Dextrose 2.5%/ Sodium Chloride 0.45% Potassium Chloride 20mmol/ 1000mL Magnesium Sulphate 10mmol/ 1000mL Calcium Chloride 0.6mmol/ 1000mL Total Volume:2250mL/m^2 over 18 hours (125mL/m^2/hour) (Maximum volume 3375mL)
Day 3	**T=0**	Etoposide 150mg/m² in sodium chloride 0.9% (0.2-0.3mg/mL) over 4 hours.
Day 4	**T=0**	Etoposide 150mg/m² in sodium chloride 0.9% (0.2-0.3mg/mL) over 4 hours.

Consolidation therapy

Cyclophosphamide: 1000 mg/m^2/d given as IV infusion, over one hour, once daily, day 1 and 2

Vincristine: 1.5 mg/m^2 IV (max. dose 2 mg) - day 1 (VCR may be given as a bolus or short infusion as necessary to comply with local or national guidelines.) N.B. Vincristine must be administered by IV routes only.

MESNA: The use of MESNA should be in accordance with institutional practice to reduce the risk of urothelial toxicity. If gross haematuria occurs on Day 1, MESNA should be increased in the first instance, if previously administered, or added if not previously given. Cyclophosphamide may be omitted on day 2 at the discretion of the treating Investigator. In the following course MESNA should be given in a dose of at least 120% of the dose of cyclophosphamide with hyper-hydration. The dose of cyclophosphamide may be halved (500 mg/m^2) on both days 1 & 2 if this is considered necessary. If well tolerated the standard dose should be administered in subsequent courses with MESNA and hyper- hydration.

Recommendation: MESNA 250 mg/m^2 IV before first cyclophosphamide infusion, 750 mg/m^2/24 hour, day 1-2.

The following haematological criteria must be met prior to commencement of each cycle:

ANC ≥ 1.0 x 10^9/L or leukocytes ≥ 2.0 x 10^9/L

Platelets ≥ 100 x 10^9/L

Day & Time	Drug	Administration Fluid/Volume/Rate	Route
Day 1 T = 0 hrs	PRE-HYDRATION 375ml/m^2	Glucose 2.5% & NaCl 0.45% with Potassium 20mmol/l Infuse at ml/hr for 3 hours	IV
Day 1 T = 0 hrs	MESNA 200mg/m^2	In 50ml Sodium Chloride 0.9% Infuse at ml/hr for 3 hours	IV
Day 1 T = 3 hrs	VINCRISTINE 2mg/m^2	IV Bolus	IV
Day 1 T = 3 hrs	HYDRATION 3000ml/m^2	Glucose 2.5% & NaCl 0.45% with Potassium 20mmol/l Infuse at ml/hr for 24 hours	IV
Day 1 T = 3 hrs	MESNA 1200mg/m^2	In 96ml Sodium Chloride 0.9% Infuse at ml/hr for 24 hours	IV
Day 1 T = 3 hrs	CYCLOPHOSPHAMIDE 1000mg/m^2	In ml Sodium Chloride 0.9% Infuse at ml/hr for 60 minutes	IV
Day 2 T = 3 hrs	HYDRATION 3000ml/m^2	Glucose 2.5% & NaCl 0.45% with Potassium 20mmol/l Infuse at ml/hr for 24 hours	IV
Day 2 T = 3 hrs	CYCLOPHOSPHAMiDE 1000mg/m^2	In ml Sodium Chloride 0.9% Infuse at ml/hr for 60 minutes	IV

Assessments.

Schedule of Events

Assessments	Pre-surgery	Post-surgery	Post-RT/ prior to maintenance	Prior to each course of maintenance	During maintenance	6 weeks after end of treatment (maintenance)	2 years	5 years	
Clinical examination to include neurological exam, height and weight	●	●	●	●		●	●	●	
Magnetic Resonance Imaging (MRI) **Whole brain and craniospinal axis**	●	● Spinal MRI not necessary unless not performed pre-surgery	●		● after 3 and 6 courses	●	● Every 4 months during the first year after treatment, every 6 months during the second year after treatment, every year until 5th year after treatment[2,5]		
Central review of histology		●							
Lumbar puncture for CSF cytology		●	● if positive post surgery			● if positive post surgery	● if positive post surgery	● if positive post surgery	● if positive post surgery
Glomerular filtration rate			●	● before course containing cisplatin/carboplatin		●			

Assessments	Pre-surgery	Post-surgery	Post-RT/ prior to maintenance	Prior to each course of maintenance	During maintenance	6 weeks after end of treatment (maintenance)	2 years	5 years
Full blood count			● should be performed weekly during RT	●	● every 2 weeks			
Blood chemistry			should be performed weekly during RT		●	●		
Pure tone audiometry			●	before course containing cisplatin or carboplatin		●	●	●
Cerebellar Mutism syndrome assessment		●						
Endocrine evaluations		●				●	Should be performed at least annually	
Quality of Survival (QoS) assessments		●					●	●
Neuropsychological outcome[7]		●					●	●

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APPENDIX 1 - TUMOUR STAGING

Chang Criteria for staging of Medulloblastoma

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.
M4	Metastasis outside the cerebrospinal axis.

APPENDIX 2. STANDARD CLINICAL PRACTICE RECOMMENDATIONS IMAGING WORKING GROUP

This summary has been developed by Dr Shivaram Avula and Prof Giovanni Morana

Summary version and date: v1.3, 28.04.2021

Background

Imaging evaluation of primary tumours of the central nervous system (CNS) and possible CNS dissemination is core to their management in children. Given the infrequency of childhood CNS tumours, multicentre studies provide the best scientific evidence for their management. Standardisation of imaging acquisition therefore is an essential pre-requisite across all centres who participate in paediatric CNS tumour studies. Standardisation of imaging not only facilitates comparisons of scans for an individual subject across various time points (pre-operative, post-operative and subsequent follow-up imaging) but also aids comparability across multiple centres by the central study coordinators and designated radiologists.

The European Society for Paediatric Oncology (SIOPE) Brain Tumour Imaging Working Group has developed an imaging protocol based on consensus and evidence from earlier clinical trials. The members of the group consist of neuroradiologists, imaging scientists and clinicians with an interest in brain tumour imaging. The protocol has evolved over the past decade and is being updated in response to changes in imaging practices and the specific needs of the various clinical trials. The protocol is based on consensus among the group members either obtained in person and/or using e-mail surveys. This protocol was ratified by the group in December 2019.

The imaging protocol consists of sequences that are specific for the magnetic field strength (1.5 and 3 Tesla). Advances in MR technology have contributed to vast improvements in quality of imaging on 1.5T and 3T MR scanners. Despite these advances there is a huge variation in the capability of the scanner hardware and software across various centers. The rationale for the sequences and parameters recommended is based on practicality, published evidence where available and the reliability of tumour assessment. The protocol has been tailored to consist of the minimal essential/mandatory sequences in order to allow effective basic tumour evaluation whilst allowing for the use of additional sequences including multi-modal advanced MRI.

We have provided recommendations on advanced imaging methods including MR spectroscopy (MRS), diffusion tensor imaging (DTI) and perfusion imaging. The advanced imaging recommendations are based on studies performed by the SIOPE group members and are aimed as a guideline and are currently not mandatory.

Institutional requirements

1.5 or 3T MRI scanners

Trained imaging specialists (Radiologist/Neuroradiologist)

Trained specialists able to provide imaging under sedation/anaesthesia if required

Essential quality parameters

Designated radiologists/neuroradiologists for childhood brain tumours must be available for all patients

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Summary

Must have
All imaging studies must be performed according to the SIOPE-BTG neuroimaging protocol
Pre-OP MRI plus contrast must be available for all patients
Pre-OP 3D imaging acquisition should be done for surgery and RT purposes
Early post-OP MRI plus contrast must be available for all patients within 72h post-OP even in ventilated patients
Scans must be reported according to protocol guidelines by designated specialists with experience in paediatric neuroimaging
Desirable
Baseline spine MRI is recommended before surgical resection or biopsy, or 10-14 days after surgical resection or biopsy (to minimise postsurgical blood products and dural enhancement that might confound imaging interpretation).
During the study, at each examination, the same Tesla-strength is recommended
During the study, at each examination, comparable sequences on consecutive scans are recommended
If post-OP imaging shows extensive post-surgical changes that decrease the ability to assess residual disease, or that mimic tumour infiltration, a second follow-up MRI is recommended within 2-3 weeks after surgery.
Don’t do
Do not use CT for standard brain imaging in any childhood cancer tumour

IMAGING PROTOCOL FOR PATIENTS IN EUROPEAN SIOP BRAIN TUMOUR STUDIES

MRI protocol

Brain imaging

Essential sequences on 1.5T

Essential sequences on 3.0T

3D gradient echo (GRE) sequence is the inversion recovery GRE sequence (IR TFE/FFE)2D sequences: Slice thickness ≤ 4mm and slice gap ≤ 1mm (10 % of slice thickness is desirable).
For very small lesions consider a slice thickness of 3mm or less.
3D sequence: Slice thickness ≤ 1mm with no slice gap. An isotropic voxel resolution of 1mmx 1mm x 1mm is desirable depending on scanner capability.
Resolution parameters: Field of view – 230 mm (range 220-250 mm depending on headsize); Matrix size - minimum 256 (512 is desirable for better resolution; 96- 128 for EPI sequences).
Some centres perform T1 FLAIR, T1 inversion recovery (IR) or T1 gradient echo instead of T1 SE sequence due to its suboptimal quality on 3.0T scanners. This is acceptable as long asthe diagnostic quality of the imaging is not compromised and the same sequence is used consistently for the individual patient.
There are increasing concerns of long-term gadolinium deposition and the use ofmacrocyclic gadolinium based contrast agents is recommended.

Sequences on 1.5T that may provide additional information

Slice thickness for 3D sequences ≤ 1mm with no slice gap. An isotropic voxel resolution of1mm x 1mm x 1mm is desirable depending on scanner capability.

*3D FLAIR can be used instead of 2D FLAIR but not if 2D sequences have been used for thesame individual on previous occasions.

** The heavily weighted T2w sequence localized to a region of interest is useful in assessment of lesions (in particular poorly/non enhancing) within the extra axial space oralong the parenchymal surface.

*** Please refer to section 5.

Tumour measurement

As volumetric measurement tools are not available at all centres, the tumour volume iscalculated using the (ellipsoid volume) formula A x B x C x ½ where A, B and C are the maximum dimensions in the standard antero-posterior, transverse and cranio-caudal planes.
3D-volumetric calculations may be performed additionally. These volume calculations arethe basis for follow-up evaluation and every effort should be made to ensure the highest possible accuracy.
It is desirable to save the measurements as annotated images if possible.
If there are multiple lesions, the sum of the 5 largest lesions must be obtained. This willneed further validation and may change in the future.
Please note that the measurement guidelines may be altered in some trials where 2D measurements in the axial plane or different measurement methods for the 3 dimensionsmay be employed.

Early post-operative imaging

Optimal evaluation is made within the first 48 hours following surgery. As non-specific intracranial enhancement is often seen after 3 days following surgery the postoperative MRImust be obtained within this time. However, even within this time false positive nodular enhancement can be seen with haemostatic materials and following electrocoagulation. It istherefore prudent to carefully evaluate the pre- and post-contrast T1-weighted images in combination with the signal intensities on the T2-weighted and FLAIR sequences.

With increasing use of intraoperative MRI imaging the validity of the final intraoperative scan as baseline scan has been debated. Based on a single centre study and consensus it hasbeen agreed that the final intraoperative MRI scan is acceptable as a base line provided it is from a 3.0T scanner (as it has been only validated on 3.0T), the SIOPE brain tumour protocolis followed, supervised by radiologist experienced in children's brain tumours and reported in consensus with the operating neurosurgeon. The preoperative and final intraoperative sequences must be comparable. On occasions where there has been further resection following the intraoperative scan, this will not qualify as a final intraoperative scan. A further scan after the extended resection with the full SIOPE protocol should be performed.The final decision to use intraoperative MRI scans rests with the national reference radiologist/radiology panel as the practices vary in different countries.

Comparability with the pre-operative MRI is essential for the detection of residual tumour.The size of a possible residuum has to be measured in all three planes. If the residuum is best visible on T2-weighted images a second plane incorporating a T2-weighted or FLAIR sequence must be employed. A residuum is considered to be any area of persisting pathological signal and/or enhancement that is comparable with the appearance of the pre-operative tumour. DWI ishelpful to demonstrate any local surgical or ischaemic injury, which may influence enhancement patterns and tumour evaluation on subsequent examinations.
For the evaluation of residual tumour seen on imaging, the surgical report is often valuableand should be available.

Sequences for cranial imaging: Please refer to section 1

Follow-up MRI

Timing for follow-up MRIs should be planned according to the individual trial protocol.Please refer to section 2 regarding tumour measurements.
If the tumour enhances uniformly, the post-contrast T1 should be used for the measurement of the diameters. For heterogeneously, poorly or non-enhancing tumours thedimensions on T2/FLAIR or PD and pre-contrast T1 can be relevant. In some instances therapy related reduction of enhancement disproportionate to the change in tumour volume may be encountered. The best sequence cannot be predicted at the outset in these tumours. In these circumstances, it is useful to choose the initial sequence on which the tumour was measured or change the sequence (e.g. due to a change in contrast behaviour) and compare the tumour dimensions with the same sequence on the previous staging MRI to assess response.
In instances where the MRI findings are equivocal for tumour progression/resolution (pseudo progression/pseudo response), an early follow up scan(s) may be required to evaluate for true progression/response. When true progression is confirmed, the initial scanwhich showed the abnormality should be considered as time of progression. In the pediatricneuro-oncology setting, pseudo response mainly refers to reduction of enhancement following anti-angiogenic therapy and the response assessment in this setting is based on measurement on the T2 and FLAIR sequences.

Definition of residual tumour

The evaluation of early postoperative imaging for residual tumour can pose challenges. As very subtle residual tumours may not be visible on imaging the presence/grading of residualtumour should be made in consensus with the neurosurgical report.

Residual tumour will be defined as follows (applies only for early postoperative MRI):

R0: No residual tumour on post-operative MRI in accordance with the neurosurgical report

R1: No residual tumour on MRI but description of a small tumour residuum by the neurosurgeon or if the neurosurgical result is unknown.

R2: Small residual tumour on MRI with the maximum diameter < 5mm in any plane or thinresidual tumour covering the surgical margins like a ring or extending beyond the surgical margins.

R3: Residual tumour measurable and ≥ 5mm in all 3 planes.

R4: Size of the residual tumour unchanged or only minimally changed from the pre-operative status (e.g. after biopsy).

A thin line of enhancement can be physiological or reactive on early post-operative MRI andcorrelation with the non-contrast sequences for evidence of haemorrhage/tissue injury anddetailed comparison with pre-operative MRI may be required before considering the presence of residual tumour. If imaging is inadequate or the appearance of the surgical cavity is difficult to interpret the term “unclear” should be used. In some cases early follow up imaging in 2-4 weeks with additional sequences, better resolution parameters and additional planes may be necessary for further clarification.

Definitions for neuroradiological response evaluation:

Measurable tumours

A measurable lesion is that which can be reliably followed-up allowing for the slight variations of the scan planes. The definition of measurable lesion is based on the historic practice of using 2D measurements on predominantly 2D imaging and mainly based on the RANO criteria. The current definition is based on the assumption that 2D sequences are pre-dominantly used in a number of centers. This may change in the future when the quality of volumetric imaging is more reliable for tumour measurement and performed in all centers.

Measurable lesion:
Lesion visible in the 3 standard planes with a diameter of ≥ 10mm in each plane. This is provided that the 2D image slice thickness + gap is ≤ 5mm. If the slice thickness + gap is >5mm, then the maximum diameter should be ≥ 2 times the slice thickness + gap.

Non measurable lesion also includes lesions with poorly defined margins.

When there are multiple lesions, sum of the volumes of the 5 largest lesions are used.

Response criteria

CR (complete response): no evidence of residual or recurrent tumour or meningealdissemination.

PR (partial response): Reduction of tumour volume ≥ 50% compared to the previous staging MRI.
(The extent of meningeal dissemination can only be estimated and PR means considerablereduction of meningeal disease)

SD (stable disease): Tumour volume between ≤ 50% decrease in size and ≤ 25% increase insize compared to the previous staging MRI (no significant change of meningeal dissemination)

NOTE. MR (minor response); This criterion is used in some trials for 50% to 25% decrease intumour volume.

PD (progressive disease): increase of tumour volume of ≥ 25% or new lesion.

As highlighted in section 4, for measurable lesions, the sequence of choice for measurementcannot be predicted in advance and may require comparison of repeat measurement on themost reliable sequence on the current scan with a similar sequence on the prior/baseline scan for accurate response assessment.

Radiotherapy as a primary treatment may be associated with radiation induced reaction if there is measurable tumour growth after treatment. The combination with chemotherapy and radiotherapy may lead to temporary effects on imaging (enlarging contrast enhancing lesion, increased FLAIR/T2 abnormality) in up to 30-40% of cases, which are collectively known as pseudoprogression and may be mistaken for early true progression. If new enhancement or increase in residual tumour size occurs during the first 12 weeks after the end of irradiation and within the irradiated field, do not consider this a true progression unless otherwise confirmed (either by histology or on a short interval follow up scan – afterat least 4-6 weeks). If there is confirmed growth on the follow-up MRI, then the date of progression is ascribed to the first time point when tumour growth was documented.

Multi-Modal Advanced MRI

There is increasing experience in the use of a number of advanced MRI techniques and these may add useful information to the conventional MRI. The individual techniques shouldbe thought of as complimentary and as such a multi-modal approach is most appropriate.
We have developed and tested protocols which seek to provide a balance between quality of data and length of acquisition and at the same time give sufficient flexibility that they canbe implemented on most MR scanners. MR spectroscopy (MRS) and Diffusion Tensor Imaging (DTI) methods are well established throughout the age range and the protocols for these are fairly well agreed. However, contrast injection perfusion imaging is less well established in children. We recommend Dynamic Susceptibility Contrast (DSC) – MRI at present, although there are still some areas of active development in the protocol particularly related to the contrast injection (see section below). The current protocols for these three methods are given in the parameter table below. We do recognise that there are centres that will use more advanced protocols and would encourage anyone who is doing this or considering it to contact the SIOPE – Brain Imaging Group so that we can share experiences and further develop protocols. Examples are: 1) Arterial Spin Labelling for measuring perfusion without injecting contrast. Whilst this has generated considerable interest, we feel that further experience is required in applying this technique to children's brain tumours, in particular its relationship with DSC-MRI, prior to recommending an international protocol. 2) Multi-b value DWI and the IVIM model for measuring perfusion without injecting contrast. 3) MRS imaging to investigate the heterogeneity of tumours. 4) Functional brain connectivity via a steady state fMRI protocol especially in diencephalic syndrome. We are keen to carry out limited centre studies of such techniques.

Data Saving
It is important that data is saved in a way that it can be analysed in a quantitative manner. DICOM headers should not be altered in a manner which renders the data uninterpretable, which can happen when images are sent to some PACS systems or anonymised. Please seekadvice if you are unsure.

Contrast Injection
For DSC-MRI, contrast (usually Gd-DTPA or Gd-DOTA) injection should be via a pump injector. Most centres will not use these via a central venous line and so injection will needto be via an intravenous cannula placed prior to the scan. In order to reduce the T1 effectswe recommend giving a pre-bolus injection which is half of the full amount (i.e.
0.05mmol/Kg Gd) at least 2 minutes prior to the main injection which should also be 0.05mmol/Kg Gd, so that the total dose is 0.1mmol/Kg Gd. The rate of injection is standardised at 3ml/sec. This protocol has been used successfully in infants although there can be problems with the pump injector in very small ones, the protocol is subject to furtherdevelopment particularly in this age group.

Multimodal Protoool 22/09/2016 Version 2.3 SIOPE Brain Imaging Group

Core Multimodal Protocol (Brain)

Modality		**MRS**			Diffusion				Perfusion			
Oe scription		SVS(short-TE)			DI i				DSC- Ti♦			
Sequence		PRESS			EPI				GRE			
		Param	Value	Value	Param	Value	Param	Value	Param	Value	Param	Value
Fixed		Field	1.5 T	3 T	Field	1.ST	Field	3T	Field	1.ST	Field	3T
		TR (ms)	1500	**2000**	FOV (mm)	240	FOV (mm)	211	FOV (mm)	240x240x95	FOV (mm)	240x240x10!
		Vector length	2048	2048	Aeq matrix	96x96	Aeq matrix	96x96	Aeq matrix	96x96x19	Aeq matrix	96x96x30
		TE (ms)	30		Resolution	2.5 isotropie	Resolution (m	2.2 isotropie	Orientation	axial	Orientation	axial
					Coverage	whole brain	Coverage	whole brain	Sense	2	Sense	2
					b factor	**1000**	b factor	**1000**	Temp resoln	1.49x60	Temp resol	I.86sx60
Variable		TE (ms)		30 · 35	TR (ms)	min	TR (ms)	min	Sequenee	FE·EPI	Sequenee	FE·EPI
		VOI (ml)	3.4 · **8** (to fit tumour)	2.2 · 8 (10 fit tumour)	TE (ms)	min (fix BW?)	TE (ms)	min (fix BW?)	TE (ms)	40ms	TE(ms)	40ms
		BW (kHz)	2 or 2.5 kHz	2 or 2.5 kHz	Grad dirs	15+	Grad dirs	15+	TR (ms)	min	TR(ms)	min
		Aves(WS)	128 · 256	64 · 196	NSA(b=O)	1(3)	NSA (b=O)	1 (3)	fti p angle	20 deg	fli p angle	20 deg
		Aves (W)	**8** · 16	**8** · 16	Speed·up	x2	Speed·up	x2	Injection rate	3ml/s,e	Injection ra1	3ml/s,e
					Partial Fourier		Partial Fourier		Gd·DTPA	O.lmmol/Kg 50% as pre bolus	Gd·DTPA	O.lmmol/Ki 50% as pre bolus
Time (mins)	Set-up		3	3					2		2	
	Acq		3.4 · 6.6	2.3 · 6.7					2		2	
	Total		6.4 · 9.6	5.3 · 9.7	5		3		4		4	
	Total	minimum at 3T - 8.3 mins + DSC										

PET imaging

There is growing interest and evidence in the use of PET imaging to assess brain tumours in children at diagnosis and /or surveillance. The following section aims to serve as a guidance for the usage of PET in pediatric brain tumours.PET imaging can supplement MRI using an amino acid tracer as O-(2-[^{18}F]fluoroethyl-L-tyrosine (FET), L-[methyl- ^{11}C]methionine (MET),or 3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalamine (FDOPA). 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) is a less useful tracer due to the high uptake in normal grey matter and will not be mentioned further. Four hours of fasting is recommended before tracer injection to ensure stable metabolic conditions. The use of a head holder is recommended to avoid motion artifacts.

Tracer	Dose MBq/kg	Examples of Scan times	Background region (healthy tissue)	Tumour-to background ratio	Physiological uptake
FET	3	20-40 min p.i. or 0-40 min p.i. (dynamic)	Cortical non-affected GM and WM	>1.6 (or >1.8)	Vascular structures, cerebellum, skin, basal ganglia, pineal body, venous anomaly
MET	10	10-30 min p.i. /20-40 min p.i.	Cortical non-affected GM and WM	>1.3	
FDOPA	3	15-45 min p.i.	Contralateral striatum	>1	Basal ganglia, pituitary, skin, pineal body, venous anomaly
			Cortical non-affected GM and WM	>1.6	

p.i.: post injection, GM: grey matter, WM: white matter

Iterative reconstruction should be applied or alternatively filtered back projection. Corrections for attenuation, scatter, randoms, dead time, and decay should be applied. Theuse of point-spread-function reconstructions may give rise to artefacts and is not recommended. Voxel size < 3mm in all directions and a spatial resolution < 6 mm FWHM is recommended.

PET scans are co-registered to a recent (ideally < 2 weeks) MRI preferentially T1W + contrastor FLAIR. Note that automatic co-registration systems may introduce errors in children.
Integration of information obtained by MRI and PET should be performed by diagnostic imaging specialists in close collaboration of each other in order to offer clinicians a more comprehensive array of data. Tracer uptake is reported as maximal tumour-to-backgroundratio (TBRmax) and metabolic active volume. In case of DOPA PET maximal tumor-to-normalstriatum ratio (TSRmax) should also be reported. Increased uptake can be seen in inflammatory lesions and after epileptic seizures.
For dynamic FET: an analysis with extraction of tumour time-activity-curves is possible andmay be compared to that of healthy brain. The classification into increasing, decreasing orplateau may support the differentiation between inflammatory changes and tumour.