Medulloblastoma in Adults

Treatment Protocol

Update 2023-24 because of opening EORTC 1634 PersoMed I study.

Dutch neuro-oncology society
(Landelijke Werkgroep Neuro-Oncologie, LWNO)

Comprehensive Cancer Centre the Netherlands (IKNL), Utrecht

version June 2024

1 Working group

Chairman

J.E.C. Bromberg, MD, PhD, neurologist, Erasmus University Medical Center, Rotterdam, j.bromberg@erasmusmc.nl

Working group members

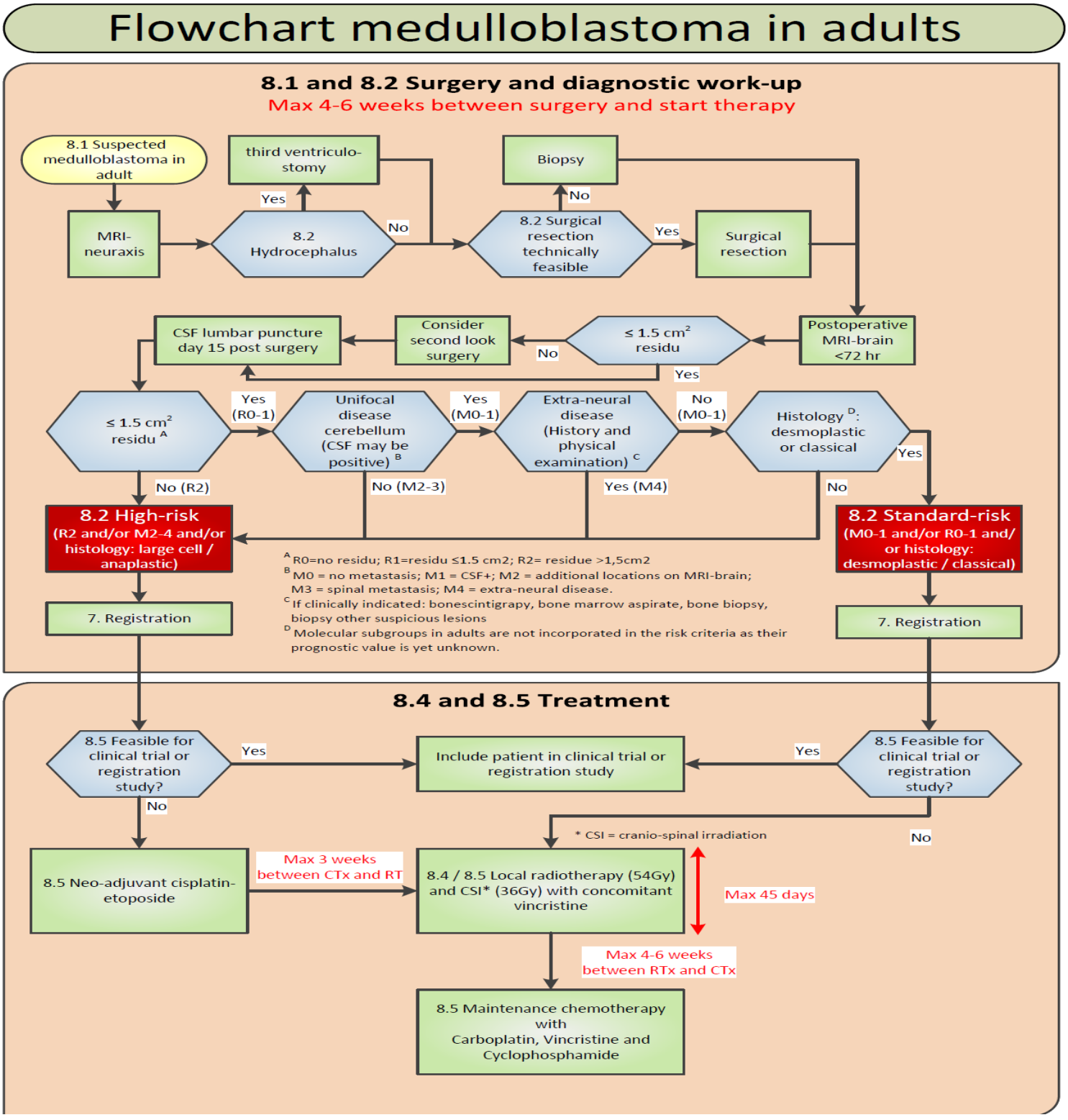
- J.M.M. Gijtenbeek, MD, PhD, neurologist, Radboud University Nijmegen Medical Centre, Nijmegen, anja.gijtenbeek@radboudumc.nl
- E. Kurt, MD, neurosurgeon, Radboud University Nijmegen Medical Centre, Nijmegen, erkan.kurt@radboudumc.nl
- C.C.D. van der Rijt, MD, PhD, medical oncologist, Erasmus University Medical Center, Rotterdam, c.vanderrijt@erasmusmc.nl
- C. Van Rij, MD, radiation oncologist, Erasmus University Medical Center, Rotterdam, c.vanrij@erasmusmc.nl
- W. Taal, MD, PhD, neuro oncologist, Erasmus University Medical Center, Rotterdam, w.taal@erasmusmc.nl
- F.Y. de Vos, MD, PhD, medical oncologist, University Medical Centre Utrecht, Utrecht, f.devos@umcutrecht.nl
- P. Wesseling, MD, PhD, neuropathologist, Radboud University Nijmegen Medical Centre, Nijmegen, p.wesseling@pathol.umcn.nl
- M.E. van Linde, MD, PhD, medical oncologist, Amsterdam University medical Centre, m.vanlinde@amsterdamumc.nl
- H.L. van der Weide, MD, radiation oncologist, University Medical Centre Groningen, Groningen, h.l.van.der.weide@umcg.nl

Advisor

- V.K.Y. Ho, MSc, epidemiologist, Comprehensive Cancer Centre the Netherlands (IKNL), Utrecht, v.ho@iknl.nl

2 Table of contents

3 Summary, flowcharts and time schedule



4 Background

4.1 Introduction

The term medulloblastoma was coined in 1925 when Bailey and Cushing reported clinical and pathologic features in 29 patients with "a very cellular tumor of a peculiar kind". Most of these 29 patients were children, and the tumors were usually located in the cerebellar vermis over the roof of the fourth ventricle (1). Medulloblastoma is a rare tumor in adult patients, accounting for only 1-2% of primary brain tumors in adults and with an estimated incidence of 10-20 patients per year in The Netherlands. As a consequence only retrospective studies have been published on this disease, with the exception of one small prospective, single arm study, the latest long term follow-up results of which were published in 2007 (2). Most data on medulloblastoma in adults are extrapolated from data obtained from children despite the fact that differences in the behavior of the disease and in the tolerance of treatment at different ages appear to exist. Because of the rarity of the disease prospective studies are difficult to perform. Therefore a protocol has been set up for diagnosis and treatment based on the available literature to achieve uniform treatment of adult medulloblastoma patients within The Netherlands and allow prospective toxicity and efficacy data to be collected for a larger number of patients than is feasible in a single center.

4.2 Pathology and Molecular characteristics

Pathology of medulloblastomas

Medulloblastomas belong to the overarching group of embryonal tumors of the central nervous system (CNS), i.e. tumors characterized by (very) high cellularity, densely packed and poorly differentiated appearing small cells often showing limited cytoplasm, variable nuclear pleomorphism and marked mitotic activity. Tumors with this phenotype in the posterior fossa are traditionally called medulloblastomas. In the 2007 (i.e. 4th) edition of the WHO classification of CNS tumors subgroups of medulloblastomas were histologically defined (3). In the last decade however, revealed particular molecular medulloblastoma subgroups and showed that combination of molecular and histological data provide complementary, clinically relevant diagnostic information. In the WHO 2016 CNS tumor classification (i.e. the updated 4th edition) medulloblastoma were defined based on both molecular or histological characteristics(4-6). With the publication of the 5th edition of the CNS WHO classification in 2021, this shifted to subclassification of medulloblastoma based on molecular features primarily, moving the histological subtype to the histological description in the integrated diagnosis (34185076). However, since there is association between the histological subtypes and the molecular features of medulloblastoma, determination of the histological subtype remains the first step of the pathological assessment.

Histological subtypes

The histologic medulloblastoma subtypes described in the CNS5 WHO 2021 classification have not substantially changed compared to the 2016 and 2007 classifications. The ***classic*** phenotype is by far the most frequent histologic subtype and shows bland microscopic features essentially as described above. The ***desmoplastic/nodular*** medulloblastoma is characterized by a nodular architecture, the reticulin-free nodules (often appearing as 'pale islands') surrounded by reticulin-rich desmoplasia. This subtype is closely associated with one of the SHH-activated groups of medulloblastoma (see below). An 'exaggerated' form of the desmoplastic/nodular subtype is medulloblastoma with ***extensive nodularity*** with many large nodules of more differentiated, neurocytic cells surrounded by reticulin-

fibers. The desmoplastic/nodular and especially the extensive nodularity medulloblastomas are associated with a better prognosis. A diagnostic pitfall in this context is the classic medulloblastoma with a nodular architecture but without reticulin-rich desmoplasia completely surrounding the nodules, such tumors do not qualify as desmoplastic/nodular medulloblastomas. A fourth histologic subtype is the ***large cell/anaplastic*** variant, a variant that typically shows tumor cells with (a combination of) large nuclei, prominent nucleoli, cell wrapping, many mitoses and/or apoptotic figures (3-6).

Molecular subtypes

Four molecular groups of medulloblastoma are recognized in the CNS5 WHO 2021 classification:

- ***WNT-activated***
  The tumors in this group occur especially in childhood, encompass about 10% of medulloblastomas, and generally show the classic, occasionally the large cell/anaplastic phenotype. Over 85-90% of WNT-activated medulloblastomas carry a *CTNNB1* mutation (less frequently mutations in other components of the WNT signalling pathway such as *AXIN1* and *APC,* occasionally a germline *APC* mutation). The defect in the WNT-signalling pathway results in nuclear accumulation of beta-catenin as can be demonstrated by immunohistochemistry. About 85% of the tumors in this group show monosomy for chromosome 6. Children with WNT-activated medulloblastomas generally have an excellent prognosis, in adults the prognosis is less favorable (7-9).
- ***SHH-activated & TP53-wildtype***
  About 30% of the medulloblastomas belong to the SHH-activated group, the vast majority of these are *TP53*-wildtype. The nodular/desmoplastic and the (much less frequently occurring) extensive nodularity histologic subtype (almost) exclusively are found in this molecular group. SHH-activated & *TP53*-wildtype tumors occur predominantly in infants and adulthood and are considered low risk, and especially in younger patients *PTCH1* or *SUFU* germline mutations may be found.
- ***SHH-activated & TP53-mutant***
  A small percentage of SHH-activated medulloblastomas is *TP53*-mutant, these tumors occur predominantly in childhood, often show the large cell/anaplastic phenotype and carry a poor prognosis. Up to half of the patients in this group have a *TP53* germline mutation (10).
- ***non-WNT/non-SHH***
  This last category encompasses the group 3 and group 4 molecular category as recognized in multiple studies that can be further subdivided into 8 subgroups (11) (representing resp. about 20% and 40% of all medulloblastomas and occurring especially in infancy/childhood). As in many centers worldwide demonstration of these subcategories is so far difficult due to a lack of easily accessible diagnostic tools, group 3 and group 4 are still included under the umbrella of the non-WNT/non-SHH molecular category in the WHO 2016 classification (4). Histologically, these medulloblastomas are almost always of the classic or large cell/anaplastic phenotype.

Preferably a methylation array analysis is performed on tumor material of all patients.
Assessment of the molecular subtype of medulloblastoma can to a certain extent be achieved by performing immunohistochemistry for (surrogate) markers like beta-catenin, GAB1, YAP1, p53, OTX2 and/or p75NGFR (12). More accurate assessment that includes (provisional) subgrouping of the molecular subtypes, however, is performed by methylation array investigation of the epigenetic profile of medulloblastoma (11, 13). This analysis may be supplemented by NGS-analysis and transcriptomic analysis to confirm the presence of specific mutations, genefusions and/or gene expression levels associated with the molecular subtype.

4.3 Clinical prognostic factors

The staging process of medulloblastoma is based on the knowledge of favourable and adverse prognostic factors and is based on the clinical prognostication score developed by Chang (14). The Chang staging system describes the extent of tumour infiltration (T1-4) and metastases (M0-4) where M0 denotes no metastases, M1 microscopic seeding in the CSF, M2 gross nodular seeding intracranially, M3 gross nodular seeding spinally and M4 extraneural metastases. Treatment in children is tailored to risk factors with a division into standard risk and high risk categories. Data on these prognostic factors are scarce in adult medulloblastoma,

The risk profile is composed of information about the stage of the disease determined firstly by investigating metastatic and / or residual disease and secondly by histopathologic classification of the tumor; this latter aspect has been outlined in the previous section (4.2).

The degree of tumor resection is related to outcome of medulloblastoma, where 5 year PFS in patients more than 3 years of age was 78% in children with tumor residue < 1.5 cm2 and 53% in patients with larger tumor residue (15). In adults, the advantage of gross total resection has also been shown in a cohort of 454 patients analyzed within the SEER database (16).

The prognostic relevance of metastatic disease in adult patients has been confirmed in some but not all studies. In the analysis of 454 patients reported by Lai (16) and 251 patients reported by Padovani et al (17) and the observational study by Von Bueren et al (18) metastatic disease conferred a worse prognosis with the exception of M1 disease. However, in the meta-analysis by Kocakaya (19) concerning 96 patients with sufficient data and in the multicenter retrospective series by Atalar (20) metastatic stage did not influence prognosis on multivariate analysis. ,Therefore, patients with M1 disease will be considered standard risk in this protocol, though accurate identification of leptomeningeal spread remains of utmost importance.
The time point to study lumbar CSF in this protocol is set at day 15 after surgery to prevent contaminating non-vital cells post-surgery with an accepted delay of up to 3 days later.
Extraneural disease is an exceptional event, but should not be overlooked in the staging procedure. In case of complaints or abnormalities on physical examination additional imaging procedures should be performed to rule out extraneural metastases.
In line with the available literature, both pathological and clinical prognostic factors will be used to categorize patients as standard or high risk.

4.4 Surgery

The surgical management of medulloblastomas has two goals. The first goal is to ameliorate the symptoms of obstructive hydrocephalus, and the second goal is to achieve maximal surgical resection (21). Controversy exists regarding the initial management of patients with a medulloblastoma. Some neurosurgeons advocate shunting the hydrocephalus routinely as the first step before tumor removal. They claim that there is lower morbidity and mortality and a better surgical field after the intracranial pressure is relieved for a period of several days to a few weeks. A disadvantage is potential dissemination of tumor cells to the peritoneal cavity or systemically after shunting: in some studies an incidence of up to 19% of extracranial metastasis has been reported (22). A second problem with early shunting is that decreasing the pressure in the supratentorial system by draining the hydrocephalus can produce an upward herniation of the tumor, which would necessitate an emergency decompression of the posterior fossa and removal of the mass. Endoscopic perforation of the floor of the third ventricle

may alternatively be performed, which provides internal shunting without the risk of extradural seeding. Furthermore, this leads to more gradual decrease of intracranial pressure and is perceived to have a lower risk of upward herniation. Others prefer to treat the increased intracranial pressure with large doses of corticosteroids for a short period of 2-3 days before surgical intervention instead of shunting. This usually produces a remarkable improvement in the symptoms and often the results of neurological examination will revert to normal.

In the paediatric setting, the extent of resection has been shown to be of prognostic importance (15), and although there is a lack of such data in adults, it is accepted that extent of resection is also a prognostic factor in adults (23). Immediate postoperative imaging (within 72 hrs) is necessary to define the extent of resection, since intra-operative judgement of residual tumor is insufficiently reliable. Second-look surgery (defined as reoperation within 2 weeks after the first surgery, aimed at resection of residual tumor) may improve survival by reducing the tumor residue, but the morbidity of the procedure is not known. There are no prospective studies on this topic, only case reports have been published in which this protocol was used (24). Although the extent of resection has been shown to affect survival, only one study has specifically addressed second look surgery. The authors conclude that second-look surgery has an acceptable morbidity and should be considered in patients with residual tumors (25).

4.5 Radiotherapy

The basis of medulloblastoma treatment consists of surgery followed by radiotherapy. Being a radiosensitive tumour, clinical and radiological response can be observed shortly after start of treatment. Because of the high propensity of medulloblastomas to disseminate within the subarachnoidal space, the radiotherapy treatment volume should always include the entire craniospinal axis, even in absence of metastatic disease (26).

Timing and overall treatment time
Several studies have shown improved posterior fossa control and/or survival after shorter intervals between surgery and start or completion of radiotherapy (27-29). Therefore, the start of radiotherapy should be within 4-6 weeks post-surgery. And the radiotherapy should be delivered 5 x / week, with minimal interruptions, an overall treatment time of less than or equal to 45 days was therefore proposed (28, 30, 31).

Technique
The radiotherapy techniques most commonly used are 3D conformal therapy (3D CRT) or intensity modulated therapy (IMRT) including volumetric arc therapy (VMAT), using photons as the radiation delivery vehicle. In most scientific publications on the treatment outcome of medulloblastoma the radiotherapy is photon-based. Because, however, photons have an exit dose, treating the entire spine results in dose to almost every organ, including a large volume of the red bone marrow compartment. The hematological toxicity can interfere with treatment (and chemotherapy) tolerability.
In recent years proton therapy has gained significant ground worldwide and is now available in hospital-based settings. As from January 2018 proton therapy is available in The Netherlands. Due to the unique properties of protons, where there is no exit dose, significant treatment related toxicity (including hematological toxicity and likely late adverse effects such as reduced fertility, cardiovascular morbidity, endocrinopathies and secondary malignancies) due to dose outside the targetvolume can be avoided (32-35). The effects of proton therapy on the tumour are similar (36, 37). This makes proton therapy the preferred radiation modality for medulloblastoma patients.

In case of recurrence or residual disease, re-irradiation with (hypofractionated/radiosurgical) stereotactic radiotherapy results in good local control without significant toxicity (38).

In conclusion, craniospinal irradiation (preferably proton-based) is an essential part of the primary treatment of patients with medulloblastomas. The interval between surgery and the start of radiotherapy should preferably be kept within 4-6 weeks.

4.6 Chemotherapy

In children with medulloblastoma, chemotherapy has been used for years in order to improve outcome for poor prognosis patients, or to decrease radiotherapy dose in standard prognosis patients. In adults with high-risk medulloblastoma, prognosis seems to be similar to that in children for those patients treated with both radiotherapy and chemotherapy. Adult patients with medulloblastoma treated with radiotherapy only fare worse than children in retrospective studies (28, 39). However, retrospective series of adolescents and adults with medulloblastoma suggest poor tolerance of chemotherapy, at least after craniospinal irradiation. (40, 41) In addition, increased and irreversible vincristine- induced neuropathy has been prospectively documented in adults at doses that are common in pediatric protocols (42).

Neoadjuvant chemotherapy, i.e. after surgery but before radiotherapy, has the advantage of increased tolerance because of uncompromised bone marrow reserve, and increased delivery due to the decreased blood-brain barrier after surgery. It also provides an in vivo assay of chemotherapy efficacy in patients with residual disease after surgery. Major disadvantage of neoadjuvant chemotherapy is the inevitable delay of intiation of radiotherapy. In children, randomized studies showed a disadvantage for neoadjuvant chemotherapy when an ineffective regimen was used (43), or when radiotherapy was postponed for more than 20 weeks after surgery (44).

The only prospective medulloblastoma study in adults available in 2010, when the first version of the Medulloblastoma National Treatment Protocol was written,used both neoadjuvant and adjuvant treatment after radiotherapy in high-risk patients. Not only was prognosis exceptionally good and comparable to that in children in this phase II study, but also toxicity appeared to be acceptable (2, 45). Apart from manageable haematological toxicity, the main problems arose from otovestibular and neurological side-effects of cisplatin.

Given the data mentioned here, treatment of adult patients with poor-risk medulloblastoma with chemotherapy in adjunction to radiotherapy seems warranted, although direct extrapolation of childhood protocols is not feasible. In order to both deliver adequate dose-intensity chemotherapy and to manage toxicity, substitution of cisplatin with carboplatin was proposed, as well as introduction of two courses of neoadjuvant chemotherapy before radiotherapy. The efficacy of carboplatin combined with etoposide in medulloblastoma is well established, in both neoadjuvant and adjuvant setting (46-48). After treatment of 16 patients with this neo-adjuvant schedule in the first version of the protocol, myelotoxicity was impressive, and led to both postponement of the second course, and postponement of the start of radiotherapy (oral communication, unpublished data). It was therefore decided to switch to cisplatin for the neo-adjuvant courses, as no severe ototoxicity, nor neurotoxicity and less myelotoxicity is to be expected. For the maintenance courses adjuvant carboplatin was kept as part of the protocol, in order to prevent ototoxicity and neuropathy (after radiotherapy). During radiotherapy, vincristine dose is limited to fortnightly rather than weekly doses in order to prevent irreversible neuropathy.

After radiotherapy, four courses of maintenance chemotherapy will be administered according to the well-tested arm B of the Children"s Oncology Group (COG) Study A9961 (49), albeit with the substitution of carboplatin for cisplatin, and a 25% dose reduction of the cyclophosphamide dose in order to prevent dose delays due to myelopsuppression. The total number of six courses (two neoadjuvant and four after radiotherapy) is equivalent to that in the small prospective phase II study of Brandes et al. (2), and to what is common to all pediatric schedules.

Thus, for this protocol the principles of successful childhood medulloblastoma treatment have been adapted to what is considered feasible in adults with medulloblastoma. Prospective registration of treatment and toxicity data will establish whether this strategy can and will be justified by patient outcome.

Addition 2018 and later: Review of recent literature
In a retrospective analysis of 43 patients with standard risk medulloblastoma, all 15 patients treated with chemotherapy in addition to resection and craniospinal irradiation were alive after a median follow-up of 10 years, whereas 78.6% of those treated without chemotherapy survived 10 years (50). Feasibility of chemotherapy treatment in standard risk adult medulloblastoma patients was demonstrated in the German prospective HIT study, but survival data are difficult to interpret given the absence of a comparative group (51).

Analysis of the 32 patients treated with the Dutch National Treatment Protocol between 2010 and 2018, showed better survival in high risk patients than in standard risk patients (5 yr PFS 90% vs 69%; 5 yr OS 90% vs 81%), though the difference was not significant. In this protocol, standard risk patients were treated with craniospinal irradiation only and high risk patients were treated with neoadjuvant carboplatin/etoposide chemotherapy, concomittant vincristine every other week with the craniospinal irradiation and adjuvant carboplatin/vincristine/cyclophosphamide (52).

Kocakaya et al performed a meta-analysis of studies regarding adult medulloblastoma (19). They found a median overall survival of 65 months; presence of metastases at diagnosis was not a significant prognostic factor. Patients receiving chemotherapy at first-line, however, survived significantly longer (mOS: 108 mo, 95% CI: 68.6–148.4) than patients treated with radiation alone or with chemotherapy only at recurrence (mOS: 57 mo, 95% CI: 39.6–74.4). In this paper it was not possible to differentiate between adjuvant and neo-adjuvant chemotherapy, nor between specific types of chemotherapy. Kann et al used the US National Cancer Database to identify patients aged 18 years and older diagnosed with medulloblastoma between 2004-2012 and underwent resection and craniospinal irradiation. With a median follow-up of 5.0 years, estimated 5-year OS was superior in patients receiving CRT versus RT (86.1% vs 71.6%, $P < .0001$). On multivariable analysis, after controlling for risk factors, CRT was associated with superior OS compared with RT (HR: 0.53; 95%CI: 0.32–0.88, $P = .01$). On planned subgroup analyses, the 5 year OS of patients receiving CRT versus RT was improved for M0 patients ($P < .0001$), for patients receiving 36 Gy CSI ($P = .0007$), and for M0 patients receiving 36 Gy CSI ($P = 0008$) (53).

Rationale for amendment to the current protocol in 2023-24
Given the above results, improved survival with the addition of chemotherapy to resection and craniospinal irradiation in standard risk medulloblastoma seems likely, although it remains to be seen whether this holds true for all medulloblastoma subgroups (4).

In the multicenter prospective, pilot NOA-7 study, 30 adult medulloblastoma patients were treated with craniospinal irradiation, weekly concomitant vincristine and up to 8 adjuvant cycles of cisplatin,

lomustine and vincristine (54). Toxicity was considerable and though 70% of patients tolerated at least 4 cycles of treatment, all needed dose modifications.

The above data support the use of chemotherapy in all medulloblastoma patients and though risk categories are still likely to be relevant, no studies can guide as yet for differential treatment. This holds true for both conventional risk categories and for molecular subgroups. The PersoMed I EORTC study aims for personalized and risk-adapted treatment for post-pubertal and adult medulloblastoma patients with M0 or M1 disease. In this study SHHa medulloblastoma patients with M0/M1 disease will be randomized for the addition of sonidegib, a hedgehog inhibitor, to standard chemo- and radiotherapy. WNT, SHHa and group 4 medulloblastoma patients with M0 disease will moreover be randomized for standard or reduced dose craniospinal irradiation. It is anticipated that a majority of Dutch patients will be enrolled in this study.

Patients with metastastic M2+ disease may be referred to the Prinses Maxima Center for participation in the SIOP high risk medulloblastoma study. Patients ineligible, unsuited or unwilling to participate in these studies will be treated according to this Dutch National protocol.

Chemotherapy regimen in high-risk (≥ M2) patients
In the Dutch National Protocol (52), high risk patients were treated with neo-adjuvant, concomitant and adjuvant chemotherapy. Some studies suggest neo-adjuvant chemotherapy may compromise survival, likely as a result of delaying radiotherapy. Table 1 shows available results from the published literature. Since no comparative studies have been performed, results from the Dutch national protocol were at least comparable to other studies, the good organization of treatment in The Netherlands allows rapid initiation of treatment, and since continued application of the same treatment protocol will allow better data regarding this treatment, it was decided to maintain the Dutch Protocol treatment for high risk patients and for those not being treated in the PersoMed I study.

Table 1. chemotherapy in high risk medulloblastoma

Author	Title	N=	Age	Chemotherapy	PFS	OS
Bleeker 2023	LWNO	12	18-46	Neo+adj	5j 90%	5j 90%
Beier, 2018	NOA-7 ALLEEN M0-1	30	>21	Alleen adj	3j EFS 67%	3j 70%
Moots, 2016	Ecog-acrin	11	>21	neoaduvant	5j 27%	5j 55%
V Bueren, 2015	HIT 2000 metastastic	23	>21	Neoadj or maintenance observational	4j EFS 52%	4j 91%
Brandes	prospective	26	18-57	Neo + adj	5j 69%	5j 73%

4.7 Follow-up

Whether surveillance-imaging improves survival in patients with medulloblastoma is strictly unknown. The only published studies specifically addressing this issue were retrospective series concerning children with medulloblastoma. However, almost all of these series show better survival after asymptomatic recurrence (10-44 months) compared to symptomatic recurrence (2-12 months) (55-59). Furthermore, recent epidemiologic data suggest similar survival in children and adults, with only infants faring worse (39). The interval between primary disease and recurrence varies greatly. In published retrospective series on adult patients, most recurrences were reported after an interval up to 6 years, with median intervals ranging from 24-50 months (17, 23, 27, 28, 60), although isolated recurrences have been reported after 18 years (23). In the only published prospective series, median PFS was 6-7 years (2).

It seems reasonable to perform surveillance imaging most intensively in the first 2 years after treatment, reducing frequency after this time and continuing surveillance until 10 years after treatment. We propose following scheme: MRI brain to be performed at 3, 6, 9, 12, 16, 20, 24 months after the end of treatment and thereafter twice a year for 3 years and yearly between 5 and 10 years after treatment. Given the data of Bartels et al, who found spinal recurrence only in combination with intracranial recurrence, routine spinal imaging seems unnecessary unless symptoms are present (59).

Evaluation of long term toxicity of the treatment should be part of the follow-up. Patients should be screened for endocrine dysfunction yearly and treated with hormone suppletion if necessary.

5. Objectives

The objectives of the current protocol are to:

1. treat all adult medulloblastoma patients in The Netherlands through a comprehensive protocol based on available published data, with separate strategies for standard-risk and high-risk tumors;
2. document the feasibility of this treatment protocol by recording side-effects and actually administered treatment in a standardized fashion;
3. document the outcome of adult medulloblastoma in EFS and OS after treatment in this standardized treatment protocol;
4. collect tumor material for translational research studies.

To this end, all patients will be prospectively registered in a central database.

6. Eligibility for registration

a. Inclusion criteria

- pathological diagnosis of medulloblastoma, whenever possible confirmed by central review (see also section 8c)
- age $\geq$ 18
- ineligible for or unwilling to participate in prospective clinical studies

b. Exclusion criteria

- pregnancy

7 Registration

Since registration bij IKNL is no longer possible it is currently performed at Erasmus MC. After diagnosis and informed consent please fill out a (brief) registration form:
https://lwno.nl/media/1130/registratieformulier-lwno_zeldzame-tumoren_v3-23-03-2022.pdf
and send it to neuro-oncotrials@erasmusmc.nl

At least the following information should be registered for each patient: date of birth, sex, patient hospital registration number, treating physician, date of diagnosis and date of registration.

8 Treatment

8.1 Diagnostic work-up and Risk profile

Staging of disease and categorization into standard or high-risk will be performed according to the following table:

Table 1. Risk profile for medulloblastoma in adults

Investigation		Standard-risk	High-risk
1. MRI brain and myelum with contrast		unifocal disease cerebellum	M2-3
2. Within 72 hr postoperative MRI brain	*If > 1.5 cm^2 consider second look surgery*	R0 R1≤ 1.5 cm^2 residu	R2 (after second look surgery)
3. History and physical examination	*If clinically indicated bonescintigrapy, bone marrow aspirate, bone biopsy, biopsy other suspicious lesions*	M0	M4
4. Histology*		desmoplastic classical	large cell/anaplastic
5. CSF lumbar puncture day 15 post surgery		M0,M1	≥M2

Residual disease: R0 = no residual cerebellar tumor; R1 = residual tumor ≤1.5 cm^2; R2 = residual tumor > 1.5 cm^2
Metastatic disease: M0 = no metastasis; M1 = tumor cells in CSF at day 15; M2 = additional tumor locations in the brain on MRI; M3 = spinal metastasis; M4 = extra-neural disease.
*Prognostic value of molecular subgroups in adults is as yet unknown. Therefore these are not incorporated into the risk profile.

In addition at baseline full blood counts, liver and renal function, electrolytes and blood glucose concentration should be performed. Other investigations are performed when required.

8.2 Treatment with neurosurgery

The surgery is usually performed with the patient in the prone position, allowing good visualization of the region of the cisterna magna, foramen of Magendie and fourth ventricle. A posterior fossa craniectomy is commonly performed, including the rim of the foramen magnum. If necessary, the posterior arch of C1 is resected. Frequently the tumor is visible in the cisterna magna upon opening the dura mater. Sometimes, "sugar coating" of the cerebellum and arachnoid can be seen. Some neurosurgeons prefer the sitting position, although the risk of air embolism does exist. The extent of tumor resection is a prognostic factor. The surgical goal is therefore to perform total gross removal of the tumor, which can frequently be done in a piecemeal fashion, avoiding traction on the vital structures of the brain stem and cerebellar peduncles. The use of bipolar coagulation, microscope, self-retaining

retractors, a high-frequency ultrasonic aspirator, and a laser has greatly improved the chances of obtaining satisfactory removal of the tumor without damage to the surrounding structures. Furthermore, by decreasing the amount of manipulation of the structures surrounding the tumor, morbidity such as swallowing difficulties, involvement of speech mechanisms, and other cranial nerve palsies is decreased. After the tumor is removed, the floor of the fourth ventricle is inspected for infiltration, and cerebrospinal fluid is usually seen draining from the dilated aquaduct of Sylvius.

All available tumor material should be sent to the pathology department for formalin fixation or snap freezing according to the guideline in section 8c.

Since the amount of residual tumor is a factor determining further treatment and prognosis, a postoperative MRI should be performed within 72 hours post-surgery to delineate residual tumor from the postsurgical inflammatory changes that are visualized on MRI after this time. In case of more than 1.5 cm^2 residual tumor, second-look surgery (defined as reoperation within 2 weeks after first surgery) should be considered, and if judged feasible, it should be performed in order to resect this residu. However, severe morbidity as a result of surgery should be avoided since a poor performance status will compromise adjuvant treatment with radiotherapy and/or chemotherapy.

If the tumor is located in an eloquent area (for example growth into the brainstem), or in case the tumor is too large and disseminated in functional areas, biopsy is advised to confirm the diagnosis. In these cases attempts at neurosurgical removal leads to unacceptable surgical risks of morbidity and mortality.

Up to approximately 50% of patients require treatment of unresolving obstructive hydrocephaly. Since placement of a ventriculoperitoneal shunt may cause peritoneal tumor spread, third ventriculostomy is the preferred alternative.

8.3 Pathology

Collection of material for pathological diagnosis and translational research

- **Tumor tissue**
  - Formalin-fixed, paraffin-embedded tissue: Sufficient representative tumor tissue needs to be formalin-fixed and paraffin-embedded to allow for optimal microscopic (including immunohistochemical) analysis and neuropathological diagnosis
  - Snap frozen tissue: Whenever possible, at least 2 (viable) tumor fragments of 3x3x3 mm, but preferably as much as possible representative tumor tissue should be snap frozen and stored at -80 °C for translational research.
  - Unless central review is needed for clinical purposes the material may be stored locally. In time samples will be transported collectively.

- **Peripheral blood**
  - Either before operation, or at any moment when blood is sampled for other reasons from 24 hours after surgery, 1 EDTA-tube with at least 10 ml peripheral blood should be taken for translational research (esp. to allow for comparison with the molecular/genetic features in the tumor tissue sample); this tube should be stored at 4°C for 24-48 hours for transport and then stored at -80°C locally. In time samples will be transported collectively.

- **CSF cytology**
  - CSF samples at day 15 need to be prepared for optimal cytological analysis of the presence/absence of tumor cells, ideally allowing for additional immunocytochemical analysis of the samples. If possible an additional tube (2-5 ml) should be collected for translational research. Samples should be stored locally.

Review of histopathological diagnosis

Because of lack of funding, central review of histopathological diagnosis will not be standard procedure but may be be performed on indication or for research purposes.

8.4 Radiation therapy

Treatment of the craniospinal axis is a large burden to the patient, necessitating careful medical monitoring and management of toxicities. Furthermore, the technical aspects of radiotherapy planning and delivery of this target are very challenging. It is advisable to concentrate treatment delivery at a center with an experienced radiation team.

Risk group	Regimen
Standard-risk patients	radiotherapy and chemotherapy (concurrent and adjuvant)
High-risk patients	radiotherapy and chemotherapy (neo-adjuvant, concurrent and adjuvant; neoadjuvant to be skipped if, due to circumstances, likely to cause significant additional delay in start of RT

Timing of Radiation Therapy
When no neo-adjuvant chemotherapy is planned, radiotherapy should start within 4-6 weeks of surgery. In case of rapid clinical progression due to tumour an even quicker start (start with boost, photon therapy, whole brain) should be considered. The expected duration of radiotherapy is 6 weeks (30 fractions, 5 times per week).

In case of neoadjuvant chemotherapy the radiotherapy should start within 3 weeks of the second course of chemotherapy, depending on bone marrow recovery. Control of neutrophils and platelets should be performed on day 22 ±3 days and weekly thereafter, starting RT as soon as platelets > 100 x 10^9/l, neutrophils > 1 x 10^9/l

RT preparation
For accurate dose delivery and reproducibility an individual mask immobilizing head and shoulders is necessary. For accurate target delineation a registration of the post-operative MRI of the cerebrum on the planning CT is mandatory. A recent planningsMRI for boost planning (anatomical shift of resection cavity and brainstem) is advised.

Radiation technique
The preferred technique is internsity modulated proton therapy. Due to the limited availability of proton therapy, a quick start of the referral procedure is mandatory. In case proton therapy is not available or achievable the patient will be treated with photon therapy, either 3D CRT or IMRT/VMAT.
Using highly conformal advanced radiation techniques makes image guidance during delivery very important.

Target volumes
GTV primary tumor (PT): resection cavity and residual macroscopic disease as visible on recent MRI.
GTV metastases: as visible on MRI.
CTV primary tumor/focal boost: GTV primary tumor + 0.5 cm margin adapted to natural borders (ie bone, tentorium).
CTV posterior fossa (PF) boost: cranial extension: tentorium; caudal border: C1-C2; ventral: brainstem including the pre-pontine CSF space; dorsal: tentorium and occipital bone; lateral: tentorium and bone, the sigmoid sinus can be excluded. The internal acoustic canal is not included unless macroscopic disease is present.
CTV focal metastases boost: GTV boost + 0.5-1.0 cm margin adapted.

CTV craniospinal axis (CSA): the entire subarachnoidal space is included. Specific attention should be given to inclusion of the cribiform plate, temporal fossa, optic nerves, Meckel's cave and other cranial nerve foramina, the lateral extensions of the spinal nerves and the inclusion of the entire thecal sack caudally as visible on MRI.

Radiation dose and prescription

Prescription

Prescription of dose is according to ICRU-50/63 guidelines

Dose

	Standard Risk	High Risk
CTV CSA	36 Gy/CGE	36 Gy/CGE
CTV PF	NA	18 Gy/CGE (54 Gy/CGE cum)
CTV PT	18 Gy/CGE (54 Gy/CGE cum)	NA
M intracranial	NA	18 Gy/CGE (54 Gy/CGE cum)
M spine diffuse	NA	3.6 Gy/CGE (39.6 Gy/CGE cum)
M spine focal	NA	14.4 Gy/CGE (50.4 Gy/CGE cum)

Aimed overall treatment time ≤ 45 days.
Weekly control of neutrophils and platelets should be performed during radiotherapy; in case of rapid decline control should be more frequent.
Interrupt RT or switch to boost if neutrophils < 0.5 x 10^9/l, or platelets < 25 x 10^9/l

Modifications due to hematological toxicity

Thrombocytopenia

If a platelet count of < 25 x 10^9/L occurs, then radiotherapy should be interrupted. Platelet transfusions may be given when necessary according to local practices and guidelines. If the counts do not recover to > 50 x 10^9/L unsupported by platelet transfusions after one week of interruption, only the posterior fossa boost will be given and the craniospinal irradiation (CSRT) will be postponed until after completion of posterior fossa boost. If counts have not recovered to > 50 x 10^9/L by the end of boost radiotherapy CSRT may have to be abandonned.

Neutropenia

If a neutrophil count of < 0.5 x 10^9/L occurs, then radiotherapy should be interrupted and G-CSF 5ug/kg (s.c.) may be given daily to maintain a neutrophil count of > 0.5 x 10^9/L. If given, G-CSF should continue until the neutrophil count rises to > 1.0 x 10^9/L for two successive days. CSRT will restart when the neutrophil count has recovered to > 1.0 x 10^9/L whether or not the patient is receiving G-CSF. If the counts have not not recovered after one week of interruption only the posterior fossa boost will be given and the craniospinal irradiation will be postponed until after completion of the posterior fossa boost. If counts have not recovered to > 1 x 10^9/L by the end of boost radiotherapy CSRT may have to be abandonned.

Anaemia

The haemoglobin level should be maintained at a minimum level of 6.2 mmol/L RT by transfusion if necessary.

Organs at risk
ALARA (As Low As Reasonably Achievable) principle, ideally with the following maximum doses per organ at risk:
Whenever possible, without compromising CTV, attempts should be made to limit the dose to the optic chiasm and nerves to Dmax 50 Gy, the brainstem to Dmax 55 Gy (D50 as low as possible), spinal cord C1 & C2 level Dmax 5 and 45 Gy respectively, to the retina (eye) to less than 45- 50 Gy, the cochlea to 30-45 Gy, to the pituitary and hypothalamus < 45 Gy.

Image guidance and robustness
According to institutional policies.

Acute toxicity (up to 3 months after treatment)
The most important acute toxicities of the craniospinal irradiation are bone marrow suppression, headache, nausea, dermatitis, alopecia and fatigue. During radiation, patients should be monitored carefully including weekly blood counts. Toxicity resulting from the higher dose region(s) include temporary focal deficits, which may necessitate treatment with steroids.
In case of photon therapy mucositis of the GI tract can be expected.

Late toxicity (months to years after treatment, irreversible)
Whole brain irradiation can cause long term neurocognitive toxicity. The neurocognitive effects can vary in severity, ranging from mild concentration problems or short term memory loss to apathy and intellectual decline, and are not reported in great detail for the adult population.
Pituitary dysfunction can occur after dosis as low as 20 Gy, and survivors should be screened for endocrine disorders once a year.
Other long term side effects include hearing loss and fibrosis of back musculature.
In case of photon therapy reduced fertility, cardiovascular morbidity can be seen.

8.5 Chemotherapy: schedules and management

8.5.1 Chemotherapy for standard risk medulloblastoma

Adults with standard risk medulloblastoma will receive radiotherapy with concomitant and maintenance chemotherapy, but no neo-adjuvant chemotherapy. When feasible include patients in prospective clinical trials, eg PersoMed I. Otherwise, the following treatment schedule will be used.

8.5.1.a Treatment overview
All patients will receive radiotherapy with biweekly vincristine, followed by four maintenance courses of chemotherapy according to the B-arm of COG A9961 with carboplatin (rather than cisplatin), vincristine and cyclophosphamide (75% dose), supported by PEG filgrastim. Post-radiotherapy (maintenance) chemotherapy will start after recovery from radiotherapy, preferably 4-6 weeks after the last radiotherapy fraction.

8.5.1 b Dose and administration of vincristine during radiotherapy
Vincristine 1.5 mg/m^2 with a maximum of 2 mg will be administered fortnightly as an IV bolus during radiotherapy, for a total of 3 doses.

Toxicity and dose modifications of vincristine during radiotherapy
Vincristine neurotoxicity

Before *each* dose of vincristine, patients should be checked for neurotoxicity. In case of toxicity > grade 1, a neurologist should be consulted. It is recommended to err on the safe side when in doubt about continuation of vincristine or vincristine dose.

Grade 1:	continue at full dose
Grade 2 or higher:	hold dose, resume vincristine at 1 mg/m^2 (1.5 mg maximum) when resolution to grade 1, and then escalate to full dosage when symptoms resolve.

For seizures, hold one (1) dose, then reinstitute at 1.0 mg/m^2 (1.5 mg maximum) while anticonvulsants are continued. If seizures do not recur, then escalate to full dosage. Rule out syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a cause of seizures.

Vincristine gastro-intestinal toxicity

Constipation should be anticipated and promptly treated with laxatives such as magnesium or fibers, while adequate fluid intake is guaranteed. In case of ileus, vincristine dose should be held until resolution, then resumed at 1 mg/m^2 (1.5 mg maximum). Escalate to full dosage when symptoms do not recur.

8.5.1.c Maintenance chemotherapy

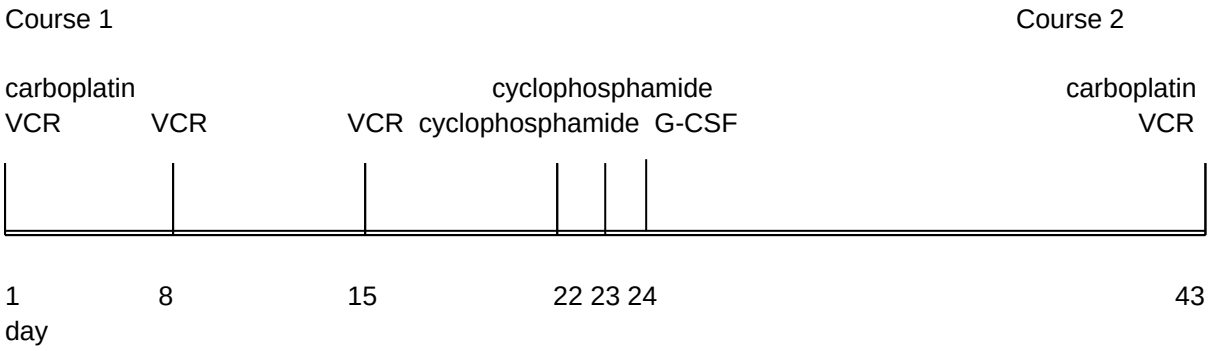
Maintenance chemotherapy should start when it is considered feasible by the treating physician, based on recovery of blood counts and performance status (which may be compromised due to fatigue, asthenia and general malaise). WHO-ECOG performance status should be 0, 1 or 2 at the start of maintenance chemotherapy. It is expected that patients will be able to start 4 weeks after the end of radiotherapy, and preferably not later than 6 weeks after the last radiotherapy fraction.

Doses and overview

Carboplatin (CBDCA): AUC 6 mg/ml,min d. 1
Vincristine (VCR): 1.5 mg/m^2 (maximum dose 2.0 mg) d. 1, 8, 15
Cyclophosphamide (CPM): 750 mg/m^2 d. 22, 23

Repeat cycle after 42 days (6 weeks), for a total of 4 cycles

Carboplatin dose will be calculated as follows:
Dose = 6 x (creatinine clearance + 25) mg. The creatinine clearance may either be measured or calculated according to the Cockroft formula.



Administration and supportive care of maintenance chemotherapy

Suggested anti-emetic regimens during maintenance chemotherapy

5HT3 antagonist (e.g. ondansetron 8 mg PO or IV or granisetron 1 mg PO or IV) prior to infusion of carboplatin (d. 1) and cyclophosphamide (d. 22 and 23)
Dexamethasone 10 mg IV prior to infusion of carboplatin (d. 1) and cyclophosphamide (d. 22 and 23)
Metoclopramide 20 mg up to 3 dd in case of nausea/vomiting

In case of intractable nausea or vomiting, dexamethason may be continued for a few days at a lower dose, as may the 5HT3 antagonist. There is insufficient proof for the use of aprepitant with this regimen.

Carboplatin administration during maintenance chemotherapy
Carboplatin will be dissolved in 500 ml glucose 5% and administered over one hour on day one of each cycle.

Vincristine administration during maintenance chemotherapy
Vincristine 1.5 mg/m^2 with a maximum of 2 mg will be administered on day 1, 8 and 15 of each cycle as an IV bolus

Cyclophosphamide administration, suggested hydration and mesna schedule during maintenance chemotherapy
Cyclophosphamide will be dissolved in 500 ml of NaCl 0.9% and administered over 1 hour on day 22 and 23 of each cycle.

Patients will be prehydrated with 1000 ml of NaCl 0.45%/Glucose 2.5% over 2 hours. After each cyclophosphamide dose 2000-2500 ml of hydration will be continued for 24 hours. Hydration fluid will contain 20 mEq/L KCl.

Mesna 500 mg (total dose) will be given 15 minutes prior to cyclophosphamide as an I.V. push. After cyclophosphamide, mesna 750 mg/m^2 will be administered, either in two doses of 375 mg/m^2 3 and 6 hours post cyclophosphamide, or continuously in the posthydration fluid.

Administration of growth factors during maintenance chemotherapy
All patients will receive PEGfilgrastim (Neulasta®) 6 mg SC on day 24 of each cycle.

Toxicity and dose modifications during maintenance chemotherapy

Hematopoietic toxicity during maintenance chemotherapy
At start of course (i.e. day 1)

At the start of each cycle of chemotherapy ANC should be > 1x10^9/L, and platelets > 100,000x10^9/L. In case count recovery is delayed then monitor counts on a weekly basis. If count recovery takes place by Day 49 (i.e. an extra week) then do not reduce the dose of cyclophosphamide. If after day 49 ANC ≥ 0.75x10^9/L, start the next cycle of chemotherapy. Maintain the same dose of carboplatin and vincristine but reduce the dose of cyclophosphamide by 25%.

If after day 49 ANC < 0.75x10^9/L and platelets < 100,000x10^9/L, then continue to monitor weekly counts (or twice weekly if feasible), and follow guidelines as outlined above for resuming chemotherapy.

If delayed count recovery continues to be a problem with subsequent cycles then reduce the dose of cyclophosphamide by 10% each time (25% initial reduction + 10% additional reduction

= 35% total reduction). If the patient requires more than 2 cyclophosphamide dose reductions, it is suggested that contact should be sought with the working group.

At day 22 (i.e. before cyclophosphamide dose)

During each cycle administer Cyclophosphamide (on Day 22 and 23) when the ANC ≥0.75x10^9/L and platelets ≥75,000x10^9/L. If there is a >1 week delay in administering the Day 21, 22 chemotherapy then reduce the Carboplatin dose to AUC 5 mg/ml,min in the next cycles. If delayed count recovery continues to be a problem with subsequent cycles, then reduce the dose of carboplatin further by 1 mg/ml,min AUC.

Febrile neutropenia

After febrile neutropenia, prophylactic antibiotics may be prescribed for subsequent courses. Carboplatin dose may be reduced by 1 mg/ml,min if febrile neutropenia re-occurs before day 21 in spite of antibiotic prophylaxis. Cyclophosphamide dose may be reduced by 25% if febrile neutropenia re-occurs after day 22 in spite of antibiotic prophylaxis.

In case of repeated dose delays ≥ 2 weeks at either day 1 or 22

If dose reductions have not succeeded in timely administration of courses, contact should be thought with the working group. Carboplatin may be replaced by cisplatin (75 mg/m^2) in such cases at the physician's discretion and in the absence of significant neurotoxicity.

Vincristine neurotoxicity during maintenance chemotherapy

Grade 1:	continue at full dose
Grade 2 or higher:	hold dose, resume vincristine at 1 mg/m^2 (1.5 mg maximum) when resolution to grade 1, and then escalate to full dosage when symptoms resolve.

For seizures, hold one (1) dose, then reinstitute at 1.0 mg/m2 (1.5 mg maximum) while anticonvulsants are continued. If seizures do not recur, then escalate to full dosage. Rule out syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a cause of seizures.

Vincristine gastro-intestinal toxicity during maintenance chemotherapy

Constipation should be anticipated and promptly treated with laxatives such as magnesium or fibers, while adequate fluid intake is guaranteed. In case of ileus, vincristine dose should be held until resolution, then resumed at 1 mg/m^2 (1.5 mg maximum). Escalate to full dosage when symptoms do not recur.

Other non-hematological toxicity during maintenance chemotherapy

All toxicity (save alopecia) should be resolved until grade 1 or less before day 1 or 22 of each course. Dose reductions due to unresolved other toxicities than those mentioned above are not foreseen, but may be necessary and executed at the physician's discretion.

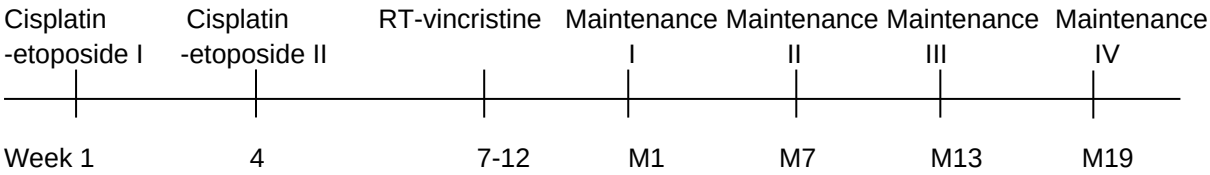
8.5.2. Chemotherapy for high-risk medulloblastoma

8.5.2.a Treatment plan overview

All patients will receive two courses of neoadjuvant chemotherapy with cisplatin-etoposide, followed by radiotherapy with biweekly vincristine, followed by four maintenance courses of chemotherapy according to the B-arm of COG A9961 with carboplatin (rather than cisplatin), vincristine and cyclophosphamide (75% dose), supported by PEG filgrastim. Neo-adjuvant chemotherapy will start as soon as the patient has recovered from surgery and staging has been completed, but preferably within

21 days after surgery. Post-radiotherapy (maintenance) chemotherapy will start after recovery from radiotherapy, preferably 4-6 weeks after the last radiotherapy fraction.
Week 1 is the start of chemotherapy treatment. Since delay after radiotherapy may vary, the start of maintenance chemotherapy is denoted as week Maint1, start of second cycle week M7 etc.

Overview of treatment schedule and time line



All drugs may be administered according to local protocol, but suggested schedules are given for administration, hydration and supportive care for all cycles.

Fertility preservation

Male patients will be encouraged to cryopreserve sperm before start of chemotherapy treatment. Female patients may be prescribed oral contraception or GH-RH agonists for the duration of treatment, in order to maximize the likelihood of preserved fertility after completion of treatment. Contact may be sought with the local fertility department to explore the possibility of vitrification-technique cryopreservation of oocytes.

8.5.2.b Neoadjuvant courses

Neoadjuvant doses

Cisplatin 80 mg/m^2 d.1 IV
Etoposide 100 mg/m^2 d.1-3 IV

Repeat cycle after 21 days, for a total of 2 cycles

Administration of neo-adjuvant chemotherapy

Cisplatin will be dissolved in 1000 ml NaCl 0.9% and administered over 1–4 hours, according to local protocol.
Etoposide will be administered in 500 ml NaCl 0.9% and administered over one hour.

Suggested premedication and supportive care for neo-adjuvant chemotherapy

Anti-emetics:
5HT3 antagonist (e.g. ondansetron 8 mg PO or IV or granisetron 1 mg PO or IV) day 1 and 2 prior to infusion of cytostatic drugs, to be repeated in the evening and on d.3 in case of nausea.
Dexamethasone 10 mg IV prior to infusion of cytostatic drugs on day 1 and 2
Metoclopramide 20 mg up to 3 dd in case of nausea/vomiting

Hydration: at least 2000 mL NaCl 0.9% per day, in addition to the fluids in which treatment is administered.
Growth factors: only in case of febrile neutropenia in the first course (see hematological toxicity)

Toxicity and dose modifications of neo-adjuvant chemotherapy

Hematological toxicity

At the start of each cycle of chemotherapy the absolute neutrophil count (ANC) should be ≥ 1 x 10^9/L, and platelets ≥ 100,000 x 10^9/L. In case count recovery is delayed then monitor counts on a

twice weekly basis. As soon as counts recover (but within 2 weeks), the second cycle is administered *at the original dose*. If febrile neutropenia has occurred, PEGfilgrastim should be administered on day 3 of the second course. No dose reduction for haematological toxicity is foreseen. In case chemotherapy has to be delayed for 2 weeks or more, the second neo-adjuvant course will not be delivered and radiotherapy will be started instead. In that (unlikely) case, an extra course of maintenance chemotherapy may be substituted at the physician's discretion.
Premenopausal females may be prescribed orgametril in case of grade 3-4 thrombopenia (i.e. platelets < 50 x 10^9/l) during treatment, in order to minimize menstrual blood loss. Because the majority of female patients will be on either oral contraceptives or LH-RH agonists, the chances of heavy menstrual bleeding seem remote.

Non-hematological toxicity
For grade 3 or 4 mucositis, the next course will be delayed until recovery to grade 0 or 1. The second cycle may be administered at 80% of the etoposide dose (i.e. 120 mg/m^2 d.1 and 2), with 100% of the cisplatin dose. All other toxicities (save alopecia) should resolve until grade 1 or 0 before the second course is started. In case of dose delay of 2 or more weeks, the second neo-adjuvant course must be cancelled and radiotherapy should start. An extra course of maintenance chemotherapy may then be substituted at the physician's discretion.

8.5.2.c Chemotherapy during radiotherapy
see 8.5.1.b

8.5.2.d Maintenance Chemotherapy
See 8.5.1.c

8.5.2.e Recommended observations during protocol treatment
Please refer to chapter 9, page 24 for required clinical observations.

8.6 Follow-up

Imaging will be performed every 3 months in the first year and every 4 months in the second year starting 3 months after radiotherapy. Thereafter imaging will be performed twice a year for 3 years and yearly between 5 and 10 years after treatment. Imaging will consist of cranial MRI only unless other localizations were present at presentation or new symptoms prompt additional or more extensive imaging.

9 Required clinical observations

Table 1. Required observations

Observation	Post-operatively	During RT (weekly)	During maintenance CT	After maintenance CT[4]	Follow-up[5]
Physical and neurological exam	X	X	Every 3 weeks	X	X
Height	X				
Weight		X	D. 1, 8, 15, 22 of each cycle		
WHO performance status	X	X	Every 3 weeks	X	X
NCI-CTC toxicity		X	D. 1, 8, 15, 22 of each cycle	X	
MRI – brain[6]	X ≤ 72 hrs of operation		Before start [and in case of residual disease after RT: also after 2nd maintenance course]	X	X
MRI – spine[6]	X			o.i.	o.i.
CSF	day 15			o.i.	o.i.
CBC	X	X	Every 3 weeks	X	o.i.
Liver function[1]	X		Every 3 weeks	X	o.i.
Renal function[2]	X		Every 3 weeks	X	o.i.
Electrolytes[3]	X		Every 3 weeks	X	o.i.
PA review	X				

*high risk patients only

[1] Bilirubin, ASAT, ALAT, gammaGT and alkaline phosphatase
[2] Creatinine and creatinine clearance calculation (or GFR)
[3] Sodium, potassium
[4] 0-14 days after day 21 of cycle 4
[5] 3, 6, 9,12,16,20, 24 months after the end of treatment. Thereafter twice a year for 3 years and yearly between 5 and 10 years after treatment
[6] for details concerning imaging protocol see appendix E

10 Data collection

Patients will be registered prospectively as described above in section 7: Registration.

All further data will be collected retrospectively on Case Report Forms (CRF) to document eligibility, safety and efficacy parameters and compliance to treatment schedules. Data collected on the CRF are derived from the protocol.

All CRF entries must be based on source documents.

11 References

1. Bailey P, Cushing H. Medulloblastoma cerebelli: a common type of midcerebellar glioma of childhood. Archives of neurology & psychiatry 1925;14(2):32.
2. Brandes AA, Franceschi E, Tosoni A, Blatt V, Ermani M. Long-term results of a prospective study on the treatment of medulloblastoma in adults. Cancer. 2007;110(9):2035-41.
3. Louis DN, Ohgaki H, Wiestler OD, Cavanee WK. WHO Classification of Tumours of the Central Nervous System. Lyon: IARC Press; 2007.
4. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol. 2012;123(4):465-72.
5. Louis DN, Perry A, Burger P, Ellison DW, Reifenberger G, von Deimling A, et al. International Society Of Neuropathology--Haarlem consensus guidelines for nervous system tumor classification and grading. Brain pathology (Zurich, Switzerland). 2014;24(5):429-35.
6. Louis DN, Ohgaki H, Wiestler OD, Cavanee WK, Ellison DW, Figarella-Branger D, et al. WHO Classification of Tumours of the Central Nervous System. Lyon: IARC Press; 2016.
7. Gajjar A, Pfister SM, Taylor MD, Gilbertson RJ. Molecular insights into pediatric brain tumors have the potential to transform therapy. Clin Cancer Res. 2014;20(22):5630-40.
8. Zhao F, Ohgaki H, Xu L, Giangaspero F, Li C, Li P, et al. Molecular subgroups of adult medulloblastoma: a long-term single-institution study. Neuro Oncol. 2016;18(7):982-90.
9. Shih DJ, Northcott PA, Remke M, Korshunov A, Ramaswamy V, Kool M, et al. Cytogenetic prognostication within medulloblastoma subgroups. J Clin Oncol. 2014;32(9):886-96.
10. Zhukova N, Ramaswamy V, Remke M, Pfaff E, Shih DJ, Martin DC, et al. Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. J Clin Oncol. 2013;31(23):2927-35.
11. Northcott PA, Buchhalter I, Morrissy AS, Hovestadt V, Weischenfeldt J, Ehrenberger T, et al. The whole-genome landscape of medulloblastoma subtypes. Nature. 2017;547(7663):311-7.
12. Pfister S, Remke M, Benner A, Mendrzyk F, Toedt G, Felsberg J, et al. Outcome prediction in pediatric medulloblastoma based on DNA copy-number aberrations of chromosomes 6q and 17q and the MYC and MYCN loci. J Clin Oncol. 2009;27(10):1627-36.
13. Capper D, Jones DTW, Sill M, Hovestadt V, Schrimpf D, Sturm D, et al. DNA methylation-based classification of central nervous system tumours. Nature. 2018;555(7697):469-74.
14. Chang CH, Housepian EM, Herbert C, Jr. An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. Radiology. 1969;93(6):1351-9.
15. Albright AL, Wisoff JH, Zeltzer PM, Boyett JM, Rorke LB, Stanley P. Effects of medulloblastoma resections on outcome in children: a report from the Children's Cancer Group. Neurosurgery. 1996;38(2):265-71.
16. Lai R. Survival of patients with adult medulloblastoma: a population-based study. Cancer. 2008;112(7):1568-74.
17. Padovani L, Sunyach MP, Perol D, Mercier C, Alapetite C, Haie-Meder C, et al. Common strategy for adult and pediatric medulloblastoma: a multicenter series of 253 adults. Int J Radiat Oncol Biol Phys. 2007;68(2):433-40.
18. von Bueren AO, Friedrich C, von Hoff K, Kwiecien R, Muller K, Pietsch T, et al. Metastatic medulloblastoma in adults: outcome of patients treated according to the HIT2000 protocol. Eur J Cancer. 2015;51(16):2434-43.
19. Kocakaya S, Beier CP, Beier D. Chemotherapy increases long-term survival in patients with adult medulloblastoma--a literature-based meta-analysis. Neuro Oncol. 2016;18(3):408-16.
20. Atalar B, Ozsahin M, Call J, Napieralska A, Kamer S, Villa S, et al. Treatment outcome and prognostic factors for adult patients with medulloblastoma: The Rare Cancer Network (RCN) experience. Radiother Oncol. 2018;127(1):96-102.
21. Zakhary R, Keles GE, Aldape K, Berger MS. Medulloblastoma and primitive neuroectodermal tumors. In: Kaye AHL, E. R., editor. Brain Tumours: An Encyclopedic Approach. London: Churchill Livingstone; 2001. p. 605-15.
22. Kleinman GM, Hochberg FH, Richardson EP, Jr. Systemic metastases from medulloblastoma: report of two cases and review of the literature. Cancer. 1981;48(10):2296-309.
23. Riffaud L, Saikali S, Leray E, Hamlat A, Haegelen C, Vauleon E, et al. Survival and prognostic factors in a series of adults with medulloblastomas. J Neurosurg. 2009;111(3):478-87.
24. Razak AR, Nasser Q, Morris P, Alcutt D, Grogan L. Medulloblastoma in two successive pregnancies. J Neurooncol. 2005;73(1):89-90.

25. Khan RB, Sanford RA, Kun LE, Thompson SJ. Morbidity of second-look surgery in pediatric central nervous system tumors. Pediatric neurosurgery. 2001;35(5):225-9.
26. Ajithkumar T, Horan G, Padovani L, Thorp N, Timmermann B, Alapetite C, et al. SIOPE - Brain tumor group consensus guideline on craniospinal target volume delineation for high-precision radiotherapy. Radiother Oncol. 2018;128(2):192-7.
27. Herrlinger U, Steinbrecher A, Rieger J, Hau P, Kortmann RD, Meyermann R, et al. Adult medulloblastoma: prognostic factors and response to therapy at diagnosis and at relapse. Journal of neurology. 2005;252(3):291-9.
28. Chan AW, Tarbell NJ, Black PM, Louis DN, Frosch MP, Ancukiewicz M, et al. Adult medulloblastoma: prognostic factors and patterns of relapse. Neurosurgery. 2000;47(3):623-31; discussion 31-2.
29. Skolyszewski J, Glinski B. Results of postoperative irradiation of medulloblastoma in adults. Int J Radiat Oncol Biol Phys. 1989;16(2):479-82.
30. del Charco JO, Bolek TW, McCollough WM, Maria BL, Kedar A, Braylan RC, et al. Medulloblastoma: time-dose relationship based on a 30-year review. Int J Radiat Oncol Biol Phys. 1998;42(1):147-54.
31. Brandes AA, Paris MK. Review of the prognostic factors in medulloblastoma of children and adults. Critical reviews in oncology/hematology. 2004;50(2):121-8.
32. Brown AP, Barney CL, Grosshans DR, McAleer MF, de Groot JF, Puduvalli VK, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. Int J Radiat Oncol Biol Phys. 2013;86(2):277-84.
33. Song S, Park HJ, Yoon JH, Kim DW, Park J, Shin D, et al. Proton beam therapy reduces the incidence of acute haematological and gastrointestinal toxicities associated with craniospinal irradiation in pediatric brain tumors. Acta Oncol. 2014;53(9):1158-64.
34. Ho ESQ, Barrett SA, Mullaney LM. A review of dosimetric and toxicity modeling of proton versus photon craniospinal irradiation for pediatrics medulloblastoma. Acta Oncol. 2017;56(8):1031-42.
35. Tamura M, Sakurai H, Mizumoto M, Kamizawa S, Murayama S, Yamashita H, et al. Lifetime attributable risk of radiation-induced secondary cancer from proton beam therapy compared with that of intensity-modulated X-ray therapy in randomly sampled pediatric cancer patients. Journal of radiation research. 2017;58(3):363-71.
36. Barney CL, Brown AP, Grosshans DR, McAleer MF, de Groot JF, Puduvalli V, et al. Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation. Neuro Oncol. 2014;16(2):303-9.
37. Yock TI, Tarbell NJ, Yeap BY, Ebb DH, Weyman E, Eaton BR, et al. Proton beam therapy for medulloblastoma - Author's reply. The Lancet Oncology. 2016;17(5):e174-5.
38. Saran F, Baumert BG, Creak AL, Warrington AP, Ashley S, Traish D, et al. Hypofractionated stereotactic radiotherapy in the management of recurrent or residual medulloblastoma/PNET. Pediatric blood & cancer. 2008;50(3):554-60.
39. Curran EK, Le GM, Sainani KL, Propp JM, Fisher PG. Do children and adults differ in survival from medulloblastoma? A study from the SEER registry. J Neurooncol. 2009;95(1):81-5.
40. Greenberg HS, Chamberlain MC, Glantz MJ, Wang S. Adult medulloblastoma: multiagent chemotherapy. Neuro Oncol. 2001;3(1):29-34.
41. Tabori U, Sung L, Hukin J, Laperriere N, Crooks B, Carret AS, et al. Medulloblastoma in the second decade of life: a specific group with respect to toxicity and management: a Canadian Pediatric Brain Tumor Consortium Study. Cancer. 2005;103(9):1874-80.
42. Verstappen CC, Koeppen S, Heimans JJ, Huijgens PC, Scheulen ME, Strumberg D, et al. Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. Neurology. 2005;64(6):1076-7.
43. Zeltzer PM, Boyett JM, Finlay JL, Albright AL, Rorke LB, Milstein JM, et al. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. J Clin Oncol. 1999;17(3):832-45.
44. Kortmann RD, Kuhl J, Timmermann B, Mittler U, Urban C, Budach V, et al. Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91. Int J Radiat Oncol Biol Phys. 2000;46(2):269-79.
45. Brandes AA, Ermani M, Amista P, Basso U, Vastola F, Gardiman M, et al. The treatment of adults with medulloblastoma: a prospective study. Int J Radiat Oncol Biol Phys. 2003;57(3):755-61.

46. Gentet JC, Doz F, Bouffet E, Plantaz D, Roche H, Tron P, et al. Carboplatin and VP 16 in medulloblastoma: a phase II Study of the French Society of Pediatric Oncology (SFOP). Medical and pediatric oncology. 1994;23(5):422-7.
47. Lopez-Aguilar E, Sepulveda-Vildosola AC, Rivera-Marquez H, Cerecedo-Diaz F, Santacruz-Castillo E, Valdez-Sanchez M, et al. Survival of patients with medulloblastoma treated with carboplatin and etoposide before and after radiotherapy. Archives of medical research. 1998;29(4):313-7.
48. Taylor RE, Bailey CC, Robinson K, Weston CL, Ellison D, Ironside J, et al. Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. J Clin Oncol. 2003;21(8):1581-91.
49. Packer RJ, Gajjar A, Vezina G, Rorke-Adams L, Burger PC, Robertson PL, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol. 2006;24(25):4202-8.
50. Franceschi E, Bartolotti M, Paccapelo A, Marucci G, Agati R, Volpin L, et al. Adjuvant chemotherapy in adult medulloblastoma: is it an option for average-risk patients? J Neurooncol. 2016;128(2):235-40.
51. Friedrich C, von Bueren AO, von Hoff K, Kwiecien R, Pietsch T, Warmuth-Metz M, et al. Treatment of adult nonmetastatic medulloblastoma patients according to the paediatric HIT 2000 protocol: a prospective observational multicentre study. Eur J Cancer. 2013;49(4):893-903.
52. Bleeker L, Kouwenhoven MCM, de Heer I, Lissenberg-Witte BI, Gijsbers AH, Dubbink HJ, et al. Medulloblastoma in adults: evaluation of the Dutch society for neuro-oncology treatment protocol. J Neurooncol. 2023;162(1):225-35.
53. Kann BH, Lester-Coll NH, Park HS, Yeboa DN, Kelly JR, Baehring JM, et al. Adjuvant chemotherapy and overall survival in adult medulloblastoma. Neuro Oncol. 2017;19(2):259-69.
54. Beier D, Proescholdt M, Reinert C, Pietsch T, Jones DTW, Pfister SM, et al. Multicenter pilot study of radiochemotherapy as first-line treatment for adults with medulloblastoma (NOA-07). Neuro Oncol. 2018;20(3):400-10.
55. Mendel E, Levy ML, Raffel C, McComb JG, Pikus H, Nelson MD, Jr., et al. Surveillance imaging in children with primitive neuroectodermal tumors. Neurosurgery. 1996;38(4):692-4; discussion 4-5.
56. Bouffet E, Doz F, Demaille MC, Tron P, Roche H, Plantaz D, et al. Improving survival in recurrent medulloblastoma: earlier detection, better treatment or still an impasse? Br J Cancer. 1998;77(8):1321-6.
57. Roebuck DJ, Villablanca JG, Maher K, Nelson MD, Jr. Surveillance imaging in children with medulloblastoma (posterior fossa PNET). Pediatric radiology. 2000;30(7):447-50.
58. Saunders DE, Hayward RD, Phipps KP, Chong WK, Wade AM. Surveillance neuroimaging of intracranial medulloblastoma in children: how effective, how often, and for how long? J Neurosurg. 2003;99(2):280-6.
59. Bartels U, Shroff M, Sung L, Dag-Ellams U, Laperriere N, Rutka J, et al. Role of spinal MRI in the follow-up of children treated for medulloblastoma. Cancer. 2006;107(6):1340-7.
60. Prados MD, Warnick RE, Wara WM, Larson DA, Lamborn K, Wilson CB. Medulloblastoma in adults. Int J Radiat Oncol Biol Phys. 1995;32(4):1145-52.

Appendix A: Common terminology criteria for adverse events

The grading of toxicity and adverse events will be done using the most recent version of the NCI Common Terminology Criteria for Adverse Events, CTCAE version 5.0.
A complete document may be downloaded from the following site:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

Appendix B: ZUBROD-ECOG-WHO Performance Status Scale

0	Normal activity
1	Symptoms, but nearly ambulatory
2	Some bed time, but to be in bed less than 50% of normal daytime
3	Needs to be in bed more than 50% of normal daytime
4	Unable to get out of bed

Appendix C: RTOG neurologic function status

0	No neurologic symptoms; fully active at home/work without assistance
1	Minor neurologic symptoms; fully active at home/work without assistance
2	Moderate neurologic symptoms; fully active at home/work but requires assistance
3	Moderate neurologic symptoms; less than fully active at home/work and requires assistance
4	Severe neurologic symptoms; totally inactive requiring complete assistance at home or institution - unable to work

Appendix D: MR imaging – minimal requirements

MRI scanner - minimally 1.0T (magnetic field strength)

MRI brain:

1. unenhanced T1W;T2W; axial; FLAIR axial or coronal.
   - slice thickness no more than 5 mm
   - DWI (diffusion) – optional
2. after gadolinium: T1 W axial; coronal, sagittal; slice thickness no more than 5 mm

MRI spine:

1. unenhanced T1W en T2W sagittal; slice thickness no more than 3 mm
2. after gadolineum: T1W sagittal; slice thickness no more than 3 mm
3. transversal slices at the level(s) of abnormalities

Appendix E: MINI MENTAL STATE EXAMINATION

Naam: Patiëntnummer:
Datum : Onderzoeker:
Visite:

Oriëntatie

1. Kunt u mij vertellen:
   - Welke dag van de week het is? …/1
   - Welke maand het is? …/1
   - Welk jaar het is? …/1
   - Welke datum het vandaag is? …/1
   - Welk seizoen het is? …/1
2. Kunt u mij vertellen:
   - Op welke afdeling u bent (in welke straat u woont)? …/1
   - In welk ziekenhuis u bent (op welk huisnummer)? …/1
   - In welke stad? …/1
   - In welke provincie? …/1
   - In welk land? …/1

Inprenting / registratie

3. Ik ga drie woorden opnoemen. Als ik ze alle drie gezegd heb, vraag ik u het rijtje te herhalen: “appel” “tafel” “stuiver” ; onthoud deze woorden goed, want over een paar minuten zal ik u vragen het rijtje te herhalen …/3

Concentratie / Aandacht

4. Wilt u van de 100 zeven aftrekken en van wat overblijft weer zeven aftrekken en zo doorgaan tot ik stop zeg?
   (herhaal eventueel driemaal als de persoon stopt, herhaal dezelfde instructie, geef maximaal 1 minuut de tijd; stop na 5 antwoorden)
   Alternatief als patiënt niet wil/kan rekenen:
   “Wilt u het woord worst spellen? Help de persoon hier evt bij zodat worst correct wordt gespeld
   Zeg dan “Wilt u het nu van achteren naar voren spellen?
   (1 punt voor elke correcte positie) …/5

Inprenting / herinnering

5. Kunt u dat rijtje van 3 woorden nog eens opnoemen?
   (1 punt voor elk goed antwoord) …/3

Taal (Benoeming)

6. Laat een pen of een potlood zien: “Wat is dit?” …/1
   Laat een horloge zien: “Wat is dit?” …/1
   (1 punt voor elk goed antwoord)

Taal (Herhaling)

7. Wilt u de volgend zin herhalen? “Nu eens dit en dan eens dat” …/1
   (1 punt als de complete zin goed is)

Taal (taalbegrip en motorisch uitvoerende functies)

8. “Ik ga u nu een stuk papier geven. Wilt u het vel papier met uw rechter hand aannemen (1 punt), het in tweeën vouwen (1 punt) en het op tafel leggen (1 punt) ? …/3

Taal (hardop lezen en begrijpen van gelezen taal)

9. “Wilt u dit lezen en opvolgen: “SLUIT UW OGEN? ” …/1

Taal (schrijven)

10. “Wilt u voor mij een zin opschrijven?”
(1 punt wanneer de zin betekenis heeft en een onderwerp en een lijdend voorwerp heeft) …/1

Constructieve praxie

11. “wilt u deze figuur natekenen? …/1
(1 punt wanneer de figuur correct is nagetekend)

(Er moet een vierkant te zien tussen de twee vijfhoeken)

TOTAAL SCORE …/30

Appendix F: Collection, preservation and transport of material for pathological diagnosis and translational research

- **Tumor tissue**
  - Formalin-fixed, paraffin-embedded tissue: Sufficient representative tumor tissue needs to be formalin-fixed and paraffin-embedded to allow for optimal microscopic (including immunohistochemical) analysis and neuropathological (molecular) diagnosis
  - Snap frozen tissue: Whenever possible, at least 2 (viable) tumor fragments of 3x3x3 mm, but preferably as much as possible representative tumor tissue should be snap frozen and stored at -80 °C for translational research
  - Samples may be stored locally until transported in bulk.

- **CSF cytology**
  - CSF samples at day 15 need to be prepared for optimal cytological analysis of the presence/absence of tumor cells, ideally allowing for additional immunocytochemical analysis of the samples. Samples may be stored locally at -80C until transported in bulk.