TEMPLATE FOR STANDARD CLINICAL PRACTICE RECOMMENDATIONS

The lay-out used in this template may be adjusted to bring the document in line with other disease specific standard clinical practice documents.

General remarks:

The recommendation for brain tumours will finally consist of a general roadmap and nine tumour specific sections for (LGG, HGG, medulloblastoma, rare embryonal tumours, ATRT, ependymoma, GCT, craniopharyngioma, CPT).

The general roadmap includes sections on neurosurgery, neuroradiology, neuropathology, radiotherapy, endocrinology, neuroophthalmology, neuropsychology, and survivorship/ quality of life.

- *Take all international European, national and working group guidelines on your tumour entity into account for this document*
- *Focus only on criteria specific for your tumour entity; general requirements, for example for neurosurgery or radiology, are mentioned in the "general roadmap".*
- *If you have general criteria in mind for different chapters, which you think are important, please add them in a separate section (as bullet points) and they can later be integrated in the general part.*
- *Besides describing what should be available/done, it is also important describe what should not be done any more (if important)*
- *Focus on first line treatment*
- *General description/ characteristics of chemotherapeutic agents will be part of roadmap – describe in this tumour-type specific part the combinations used and dose modifications in case of adverse events, toxicities or allergic reactions*

EUROPEAN STANDARD CLINICAL PRACTICE RECOMMENDATIONS

FOR EPENDYMOMA OF CHILDHOOD AND ADOLESCENCE

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1. BACKGROUND AND RATIONALE

1.1 Background

Ependymomas are a major cause of cancer related death in childhood and adolescence and few advances in improving outcomes have been realised until recently and comprise a spectrum of glial tumours that can occur along the entire neuroaxis. The WHO classification of CNS tumours 2021 requires a combination of histological and molecular features as well as tumour location for an integrated diagnosis[1]. Most ependymomas in children and adolescents are located intracranially with a peak incidence in children under 3 years of age[2]. Infratentorial location is found more often (around 70%) than supratentorial. Leptomeningeal dissemination is rare and reported in up to 10% of cases but increases at recurrence[3,4]. Ependymomas arising in the posterior fossa are molecularly divided into two distinct molecular groups, namely posterior fossa group A (PFA) and posterior fossa group B (PFB)[5,6]. The majority of supratentorial ependymomas are molecularly characterized by fusion genes involving the *ZFTA* gene (formerly *C11orf95*) and the *RELA* gene as the most frequent fusion partner. Alternative fusion partners have also been identified[7]. Supratentorial ependymomas carrying *YAP1* gene fusions are less common and mostly restricted to young children. In addition to these four molecular groups, further subgroups within these groups can be distinguished[8,9]. The clinical implication of these subgroups has to be further assessed. Molecular classification has become increasingly important for ependymoma and will be increasingly applied for patient stratification in upcoming clinical trials. Vulnerabilities to target these tumours will likely lead to a diversification of treatments for the respective groups. In children and adolescents, *ZFTA* fusion-positive and PFA ependymomas comprise the vast majority of intracranial cases. Of these, PFA ependymomas are associated with the worst outcome on current standard-of care treatments. Various treatment strategies have been applied by international study groups to ependymomas of paediatric and adolescent patients in the last decades, consisting of surgery, radiotherapy and chemotherapeutic approaches (Table I and Table II). In contrast to adults, spinal ependymomas in children and adolescents are rare. Spinal ependymomas comprise spinal intramedullary ependymomas, myxopapillary ependymomas, and *MYCN*-amplified spinal ependymomas, which constitutes a clinically aggressive group characterized by high-grade histological features as well as amplification and overexpression of the *MYCN* proto-oncogene[10,11].

Table I: Summary of literature for infants with ependymoma

Protocol (Period)	Treatments	Age (months)	Nº patients	2 y PFS [%]	5 y PFS [%]	2 y OS [%]	5 y OS [%]
CCG9921[12] (1993-1997)	Induction: 5 cycles A: VCR/CDDP/CY/VP16 or B: VCR/CBDCA/IFO/VP16 Maintenance: 8 cycles VCR / VP16/ CBDCA/CY RD or PD → RT	0-36	74	38	32	82	72
Head Start[13] (1991-2002)	Induction: 5 cycles CDDP/VCR/VP16/CY ± MTX HD-CBDCA/TTT+VP16 and PBSC RT: if < 3 years RD after treatment or > 3 years + ST residue after treatment or > 3 years + PF	0,9-105	29	35	12	70	38
VETOPEC[14] (1991-1995)	Induction: 4 cycles VCR /VP16/ HD-CY Maintenance: 3 cycles VCR+CY/VP16+CDDP/VCR+CY/VP16 +CBDCA	<48	14	29		36	
HIT87/92[15] Anaplastic (1987-1997)	SSK 87 Induction (for high risk only): PCB, IFO, VP16, MTX, CDDP, ARAC Maintenance: PCB+VCR, MTX+VCR RT: systematic when reach 3 years HIT 92: Induction: CY+VCR+ITMTX, MTX+VCR+ITMTX, MTX+VCR+IT-MTX, CBDCA+VP16+IT-MTX PD → RT	1-33	34	35	65		
BB SFOP[16] (1990-1998)	7 cycles: A: CBDCA, PCB B: VP16, CDDP C: VCR, C PD → RT	5- 62	73	33		79	
CCLG 9204[17] (1992-2003)	7 cycles: A: CBDCA, VCR B: MTX, VCR C: CY, VCR D: CDDP PD → RT	1-93	89	47	41	79	63
SJYC07[18] (2007-2017)	No metastatic: 4 cycles: HD-MTX/VCR/CY/CDDP RT focal Maintenance: CY/Topotecan alternating with monthly Erlotinib Metastatic: 4 cycles: HD-MTX/VCR/CY/ CDDP + VBL 2 cycles: CY/Topotecan Maintenance: CY/Topotecan alternating with monthly Erlotinib	≤36	54	84	70	98	88

AIEOP[19] (1994-2003)	Induction: 4 cycles VCR+MTXHD +CY alternate CDDP + VP16 or VEC RD or PD after treatment → RT	3-36	41		27		36

Table II: Summary of literature for children with ependymoma

Protocol (Period)	Treatments	Age (years)	Nº patients	2 y PFS [%]	3 y PFS [%]	5 y PFS [%]	2 y OS [%]	3 y OS [%]	5 y OS [%]
AIEOP #1[20] no residue (1993-2001)	No residue: HFRT (70.4 Gy, [2 x 1,1Gy])	3-21	46			65			82
AIEOP #1[20] residue (1993-2001)	Residue: 2 cycles VEC (VCR, VP16, CY) HFRT (70.4 Gy [2x 1.1 Gy])	3-21	17			35			61
AIEOP #2[21] No residue and grade Ⅱ (2002-2014)	RT 59,4Gy [1,8Gy]	>1	48			84			98
AIEOP #2[21] No residue and grade Ⅲ (2002-2014)	RT 59,4Gy [1,8Gy] 4 cycles VEC (VCR, VP16, CY)	<21	62			62			79
AIEOP #2[21] Residue (2002-2014)	1-4 cycles VEC +/- second look surgery + 59,4Gy + 8 Gy boost (2x4Gy)	<21	50			53			67
HIT 88/89-91 ANAPLAST.[22] (1989-1997)	7 cycles: A: CBDCA, VCR B: MTX, VCR C: CY, VCR D: CDDP PD → RT	3-16	71	70			85		
St Jude[23] (1997-2007)	(If residue 7 weeks CBDCA+VP16/VCR+CY) RT 59.4 Gy focal systematic	1-22	153	85			94		
SFCE[24] (1996-2002)	HFRT: 60 Gy [2x 1Gy] if complete removal, 66 Gy otherwise	>5	24			54			74
CCG 9942[25]	chemo +RT+ VCR, CY, CIS, VP16	3-21	84			57			71

(1995-1999)									
HIT2000[26] (2001-2011)	CBDCA+VP16/VCR+CY+/- MTX + RT [age adjusted] + adjuvant chemo if residual tumour	>1.5	296		66			84	

ARAC= cytarabine, CBDCA= carboplatin, CDDP= cisplatin, CY = cyclophosphamide HD= high dose, HFRT= hypofractionated radiation therapy, IFO= ifosfamide, ITMTX= intrathecal methotrexate, MTX= methotrexate, PBSC= peripheral blood stem cell rescue, PCB= procarbazine, RD =residual disease, PD= progressive disease, RT= radiotherapy, R= randomisation, TTT=Thiotepa, VBL= vinblastine, VCR= vincristine, VP16=Etoposide.

2. PATIENT GROUP

This document applies to the following patients:
- newly diagnosed ependymomas
- <21 years old at diagnosis.

Special modifications may be required for patients with:
- tumour predisposition syndromes (e.g., NF2)
- previous malignancies or previous chemotherapy/radiotherapy
- pre-existing disease/s prohibiting standard therapy
- pregnancy or lactation
- simultaneous participation in a clinical study

3. DIAGNOSTIC PROCEDURES

3.1 Initial diagnostics and staging:

3.1.1 Procedures performed at diagnosis:

Medical history and examination at diagnosis:
- Complete medical history
- Vital signs and detailed physical examination including pubertal stage and occipital circumference in infants
- Complete neurological examination. The most common presentation is non-specific and related to raised intracranial pressure from obstructive hydrocephalus or more chronic symptomatology as cranial nerve palsies or ataxia in intracranial ependymomas. Children with spinal ependymomas most commonly present with pain, scoliosis, and urinary symptoms
- Neuropsychologic, educational psychologic and neuropedagogic evaluation
- Otolaryngologic evaluation
- Ophthalmology assessment

Staging:

Imaging:
Pre- and early post-surgery MRIs should be performed according to European guidelines and recommendations of the Response Assessment in Pediatric Neuro-Oncology committee (RAPNO)[27,28]. Specific RAPNO recommendations for ependymomas are currently in

preparation. In case of an intracranial tumour, imaging should be complemented with a spinal MRI to identify metastatic disease that may occur in about 10%[4]. While pre-surgery MRIs are needed for staging and planning of the neurosurgical intervention post-surgery imaging evaluates the grade of resection and size and location of potential residuals. Ideally, post-surgery imaging should be performed between 24 and 48 hours following surgery[29]. Later than 72 hours, unspecific changes may hinder reliable evaluation of residuals. In case of ambiguous results, post-surgery imaging may be repeated 2 weeks following neurosurgical intervention. In the current SIOP Ependymoma II trial, risk stratification is based on resection status assessed by central imaging review. As for medulloblastomas, staging is based on the modified Chang staging system[30,31] (Table III).

Lumbar puncture:
A lumbar puncture should be performed to assess potential microscopic disease (M1) in the cerebrospinal fluid (CSF). If CSF diagnostic was not performed prior surgery, lumbar puncture should be performed 2 weeks following resection to prevent detection of cells resulting from surgical intervention.

Table III: Metastatic stage of ependymomas according to the modified Chang staging system

Metastatic stage	Description
M0	No evidence of metastatic disease
M1	Microscopic tumour cells found in CSF
M2	Gross nodular seeding in cerebellum, cerebral subarachnoid space, or in the third or fourth ventricles
M3	Gross nodular seeding in spinal subarachnoid space
M4	Metastasis outside cerebrospinal axis

Laboratory investigations at diagnosis:
- Full blood count, differential and platelet count
- Electrolytes (including Ca++, PO4, Mg++), urea, creatinine, uric acid
- ALT, AST, GGT, bilirubin
- LDH level
- Haemostasis/coagulation tests
- Neuroendocrine evaluation
- HIV antibody test and serum level of hepatitis antigens according to local/national standards.

3.2 - Pregnancy test for girls/female adolescents with signs of pubertyHistopathology

Supratentorial ependymomas with a *ZFTA* or *YAP1* fusion are demarcated from adjacent brain and composed of cells characterised mainly by round uniform nuclei often with clear cytoplasm. Pseudorosettes are not prominent in most cases, and true ependymal rosettes are rare. These tumours often have a network of branching capillary blood vessels. Calcified regions and necrosis are common. Ependymomas with a *ZFTA-RELA* fusion show nuclear accumulation of p65 and universal cytoplasmic expression of L1CAM while there is no expression of L1CAM or nuclear p65 in tumours with *YAP1* fusions[32,33]. Posterior fossa ependymomas are circumscribed tumours composed of uniform small cells with indistinct cytoplasmic borders and round nuclei. In contrast to supratentorial ependymomas, perivascular pseudorosettes, characterised by tumour cells arranged in a radial fashion around blood vessels, are almost always present while true rosettes are rare. PFA ependymomas exhibit reduction of H3 K27-trimethylation, which can be readily assessed by immunohistochemistry[34,35,9]. In myxopapillary ependymomas, there is a

radial arrangement of cuboidal to elongated tumour cells around hyalinised fibrovascular cores, with accumulation of myxoid material around blood vessels and in so called microcysts. Mitotic activity is usually low[36]. *MYCN*-amplified spinal ependymomas show pseudorosettes and can have a papillary or pseudopapillary architecture[37,11,10]. Anaplastic features are common in these tumours. In general, molecular groups of ependymal tumours show variable degrees of anaplasia and have been regarded as WHO CNS grade 2 or 3 on this basis. However the utility of grading for risk stratification has remained controversial especially because of its lack of reproducibility due to inter-observer variability[38]. Molecularly defined ependymoma has yet to be assigned a WHO grade on the basis of prospective clinical trial data. The traditional histological variants of papillary, clear cell, or tanycytic ependymoma are no longer considered as distinct subtypes[1]. There is some association of these patterns with distinct ependymoma types, e.g., clear cell patterns being observed in *ZFTA* fusion-positive tumours. An integrated diagnosis according to the WHO classification of CNS tumours 2021 requires a combination of histological and molecular features as well as tumour location[1,39].

3.3 Molecular pathology

Collaborative studies have established 10 molecular groups of ependymomas with 7 occurring in paediatric/young adult patients[6,11] (Table IV). In addition to detection methods for the distinct molecular groups outlined below, DNA methylation-based profiling can reliably identify all of these. *ZFTA* fusions may be detected by several sequencing methods, RT-PCR, interphase fluorescence *in situ* hybridization (FISH), and molecular inversion profiling[32,33,6,40,41,42,43,44,45]. Outcome data derived from retrospective studies show great variance for *ZFTA* fusion-positive ependymomas[6,46,47,48,40,41,49,18]. A homozygous deletion of *CDKN2A* is associated with poor outcome[43]. *YAP1* fusions may be identified by the same techniques as described for ZFTA[45,41,42]. These tumours are often large at diagnosis but prognosis seems to be favourable[50,40,18].

Apart from DNA methylation profiling, only immunohistochemistry showing loss of H3 K27-trimethylation may identify PFA ependymomas. In contrast, retention of H3 K27-trimethylation is characteristic for PFB ependymomas[34,35,9]. Together with MYCN-amplified ependymomas, PFA have the poorest clinical outcome across molecular groups. In PFA, gain of chromosome 1q as well as 6q loss have been identified to be associated with very poor outcome[5,6,9,51]. However, also subtypes without this alteration could have a highly unfavourable course of disease[9,52]. In most cases, PFB ependymoma have a favourable clinical outcome. However, incomplete surgical resection and loss of 13q in PFB ependymoma seem to be associated with a poor prognosis[8]. Molecular groups of spinal ependymomas can be reliably recognised by DNA methylation profiling. Spinal myxopapillary ependymomas are associated with a relatively favourable prognosis. However, complete resection can rarely be achieved. In paediatric patients, dissemination during the course of the disease is found in up to 50% of patients, especially in the course of sacrococcygeal variants[53,54,55,56]. Spinal myxopapillary ependymomas will be regarded as WHO CNS grade II according to the WHO classification of CNS tumours 2021. *MYCN*-amplified spinal ependymoma is an aggressive tumour, with poor progression-free or overall survival when compared to other spinal ependymomas. Early metastasis and dissemination throughout the neuroaxis are frequent. All patients with reported follow-up data have relapsed, despite aggressive treatment[57,37,11,10].

Table IV: Molecular groups of ependymal tumours. Groups are included in the WHO classification of CNS tumours 2021

Molecular subgroup	Genetic	Age distribution	Gender distribution	Prognosis
ST-ZFTA	ZFTA fusion-positive	Median age 8 years (range 0–69 years)	♂ < ♀	🟡
ST-YAP1	YAP1 fusion positive	Median age 1.4 years (range 0–51 years)	♂ > ♀	🟢
PF-A	H3K27m/EZHIP mutation, balanced genome	Median age 3 years (range 0–51 years)	♂ < ♀	🔴
PF-B	Chromosomal instability	Median age 30 years (range 10-65 years)	♂ > ♀	🟢
SP-MPE	Chromosomal instability	Median age 32 years (range 9-66 years)	♂ = ♀	🟢
SP-EPN	NF2 mutation	Median age 41 years (range 11-59 years)	♂ < ♀	🟢
SP-MYCN	MYCN amplification	Median age 32 years (range 12–56 years)	♂ = ♀	🔴

4. TREATMENT DETAILS

Patients should be treated in a centre for paediatric oncology according to a prospective clinical trial whenever possible. The SIOP Ependymoma II trial (phase II/III) is currently recruiting across Europe. In parallel, the Children's Oncology Group ran a phase III randomised trial (ACNS0831) to assess the efficacy of post-radiation chemotherapy in children and adolescents with ependymomas and data are being analysed[58]. Recommendations below should be applied in case inclusion criteria for treatment in one of the strata of the SIOP Ependymoma II trial are not met. It is highly recommended to collect data on patients and treatments within a registry. Beside international consensus on the clinical management of intracranial ependymoma and its molecular variants that is in agreement with guidelines below there are not yet specific treatment recommendations for distinct molecular groups.

Patients ≥12 months without (relevant) residual disease (R0-R2):

Since the role of adjuvant chemotherapy has remained unclear, patients ≥12 months without residual disease (R0-R2, table V) should receive adjuvant focal radiotherapy only (total dose of 54 -59.4 Gy in fractions of 1.8 Gy 5 times/week; total dose shall be adapted according to age, neurological condition and other risk factors such as multiple surgeries (more than 2) or hydrocephalus). Application of vincristine during radiotherapy is not recommended.

Patients ≥ 12 months with residual disease (R3-R4):

A second-look surgery aiming at complete resection should always be evaluated. Adjuvant chemotherapy (e.g., VEC (cf. 4.3 or 1-2 modified HIT-SKK cycles[59] without intraventricular MTX) may be applied until second surgery. Post-operative radiation concepts are the same as for patients without residual disease.

Patients < 12 months:

Given the contentious role of chemotherapy, adjuvant radiotherapy is also recommended for very young children. An individual bridging therapy may be applied until patients reach 12

months of age. In case of a large supratentorial tumor increasing the chance for radiation-induced long-term neurocognitive sequella, an individual bridging strategy may also be considered in children <36 months. There is some evidence for HIT-SKK as well as for stratum 3 of the SIOP Ependymoma II trial being based on results from the UKCCSG/SIOP CNS 9204 trial[17]. Intraventricular MTX should not be applied.

Table V: Residual disease stage

Residual disease stage	Description
R0	No residual tumour
R1	No residual tumour based on imaging, but small remaining lesion described by neurosurgeon; or unknown neurosurgical result
R2	Residual tumour <5mm in all diameters
R3	Measurable residual tumour in 3 planes or one diameter ≥5mm
R4	No relevant changes compared to pre-surgery imaging
RX	Presence of residual tumour cannot be assessed

Spinal ependymomas:

Gross-total resection is the therapeutic mainstay in patients with primary spinal cord ependymomas. This may be achieved in more than 50% of patients[60]. The role of adjuvant treatment on progression-free or overall survival is not yet defined[61,62,63,64]. Thus, decision on further treatment at primary diagnosis should be based on the individual patient situation but might also consider the molecular group. Retrospective data on MYCN-amplified ependymoma suggest an aggressive treatment regimen[10,11,]. In case of myxopapillary ependymomas and residual disease, patients seem to benefit from adjuvant radiotherapy[65,66,67,68]. For spinal ependymomas in association with neurofibromatosis type 2, surveillance without intervention is recommended as long as no clinical signs or symptoms are observed[69,70].

4.1 Surgery

The extent of neurosurgical resection has been the most consistent independent prognostic factor reported in the last decades[71,72,73]. A more favourable outcome of patients without residual disease and the large difference in event-free and overall survival between patients with complete versus incomplete resection have led to the concepts of more aggressive resection and even second-look surgery. Initial surgery mainly depends on tumor size, vascularity and localisation in relation to functional eloquent structures for risk stratification. Technical adjuncts such as microsurgery, neuronavigation, intraoperative neurophysiological monitoring, intraoperative imaging such as ultrasound or MRI or endoscopic assistance should be used liberately in order to prepare optimal conditions for safe but maximal possible tumor resection. In case of necessary emergency surgery a two staged approach might be planned to offer full technical support during a second elective surgical intervention. In case of residual disease, a comprehensive radiological assessment of the residual disease status in terms of tumor size and location and its relation to relevant anatomical structures is of high importance. Preferably, patients should be treated in specialised centres by experienced neurosurgeons dealing on high frequency with pediatric brain tumor patients[74].

4.2 Radiotherapy

In addition to surgery, post-operative focal radiotherapy to the tumour bed is considered the standard of care for patients with non-disseminated ependymoma to lower the risk of local recurrence[23]. Craniospinal radiotherapy should be restricted to cases with metastatic disease. Highly conformal techniques such as proton beam therapy or IMRT are preferred bearing in mind the typically young age of the patients. Proton beam therapy (PBT) is nowwidely employed in healthcare settings which have access to this radiotherapeutic modality. Dosimetric studies demonstrate a reduction in the dose to structures outside the treatment volume as compared with photons, which is postulated to reduce late effects, e.g. neurocognitive sequelae and secondary malignancies. There may also be potential for reduction in the dose to adjacent organs at risk such as the cochlea. However, there is no theoretical difference in tumour outcomes between protons and photons and hence conformal photon therapy remain a widely employed and very acceptable radiation modality. Concerns have been raised around a perceived increased risk of brainstem necrosis with PBT compared with photons but a recent large study demonstrates a 0.5% mortality from brainstem necrosis which is comparable to rates reported following photon radiotherapy[75]. In addition, any increased rates of brainstem toxicity may be attributable to a higher proportion of patients presenting with risk factors such as young age and multiple surgical interventions. The interval between surgery and radiotherapy should be 6-8 weeks. Today, radiotherapy is usually applied with doses of 54-59.4 Gy. A total prescribed dose of 59.4 Gy in 33 fractions of 1.8 Gy is recommended based on favourable reported outcomes without increase in neurocognitive late effects[76,77]. There is however no study which directly compares 59.4Gy and 54Gy. In younger children (e.g. <3 to 4 years) without residual disease and in patients with particular risk factors for brainstem necrosis (< 18 months, two surgeries or more or poor neurological status) a reduced total dose of 54 Gy should be applied. For patients with metastatic disease, a dose of 36Gy to the whole craniospinal axis with a boost to the tumour bed and intracranial metastases of 54-59.4Gy and spinal metastases to 45Gy-50.4Gy according to the discretion of the treating clinician.

Radiotherapy must be delivered using 3D image-based radiation therapy treatment planning and computer-controlled delivery technique that fulfil the following:

1. Planning CT scan acquisition with the patient in treatment position and individualised immobilisation.
2. Delineation of target volumes and critical structures (OARs) on CT after co-registration with pre-operative and post-operative MRI. The GTV-CTV margin has decreased in recent years to 0.5-1.0 mm, without evidence of increased frequency of tumor relapse[22]. Therefore, the current SIOP trial recommends 0.5mm with a reduction at the brainstem interface to 0.2-0.3mm assuming no evidence of brainstem invasion. PTV margin depends on local immobilisation and on treatment imaging policies but is generally 0.3-0.5mm.
3. Design of field arrangements to minimize dose to OARs without compromising target coverage
4. PTV coverage and reporting criteria per ICRU recommendations including dose-volume histogram (DVH)

4.3 Chemotherapy

In contrast to surgery and radiotherapy, the role of chemotherapy in the management of ependymomas remains unproven despite extensive investigation. Cohorts of paediatric patients, in which the role of chemotherapy was retrospectively analysed, failed to demonstrate a survival advantage[78]. Post-operative chemotherapy approaches in children under 3 years to delay radiotherapy in very young children has demonstrated some benefit[16,17,79]. Two international randomized trials in children are currently comparing post-irradiation chemotherapy to observation only, ACNS0831 (USA) and SIOP Ependymoma II (Europe).

Current standard chemotherapy schemes:

VEC schedule: This regimen was applied in the AIEOP protocol leading to a better local control in children with residual disease after surgery[20]. It was also used in the SIOP '99 protocol for patients with a residual tumour after surgery. The schedule consists of: vincristine (1.5 mg/m², Day 1; repeated on Day 8, 15 and 22 of the first and third course), cyclophosphamide (1 g/m² infused in 1h for 3 doses, Day 1) and etoposide (100 mg/m² infused in 2h, day 1, 2 and 3).

Myelosuppressive treatment (carboplatin and cyclophosphamide), alternated with non-myelosuppressive treatment (cisplatin and high-dose methotrexate):

The chemotherapy schedule used in the first UKCCSG/SIOP CNS 9204 trial incorporated high-dose methotrexate and comprised blocks of alternating myelosuppressive and non-myelosuppressive drugs repeated at 14-days intervals after maximal surgical resection in patients below 3 years of age without adjuvant radiotherapy. It has shown the best results published to date with a 5-year event-free survival of 42% in patients who did not have metastatic disease at diagnosis[17]. Each course lasted for 56 days and a total of seven cycles were given. Course 1; carboplatin (550 mg/m² or 20 mg/kg) over 4h and vincristine (1.5 mg/m² or 0.05 mg/kg) intravenous bolus; course 2; methotrexate (8000 mg/m² or 250 mg/kg) and vincristine (1.5 mg/m² or 0.05 mg/kg); course 3; cyclophosphamide (1500 mg/m² or 50 mg/kg) over 4h; course 4; cisplatin (40 mg/m² for 48h or 1.3 mg/kg).

HIT-SKK/and modified HIT-SKK: This treatment strategy may be used to possibly render the residual tumour more amenable for second surgery before the start of radiotherapy based on the experience of the German brain tumour trial HIT2000. SKK chemotherapy and modified SKK chemotherapy are modular chemotherapy cycles consisting of four or two blocks, respectively[59].

One regular SKK chemotherapy cycle consists of four subsequent blocks: i) SKK cyclophosphamide/vincristine, ii) SKK high-dose methotrexate/vincristine, iii) SKK high-dose methotrexate/vincristine iv) SKK carboplatin/etoposide. One modified SKK chemotherapy cycle consists of two subsequent blocks: i) SKK cyclophosphamide/vincristine, ii) SKK carboplatin/etoposide.

More details regarding chemotherapy administration are found in appendix 2.

5. LONG TERM FOLLOW-UP:

Recommended follow-up after completion of treatment is summarized in the table.

Table VI: Patient follow up after treatment

	1st year after completion of treatment	2nd year after completion of treatment	From 3rd to 5th year after completion of treatment	From 5th year after completion of treatment
Complete physical and neurological examination	Every 3 months	Every 4 months	Every 6 months	Every 12 months
Endocrine evaluation	At 1 year	Once per year	Once per year	Once per year
Hearing Function	At 6 months and at 1 year	None	At 5 years	None
Ophthalmology assessment	At 1 year	Once per year	At 5 years	None
Neuropsychological assessment	At 1 year	At 2 years	At 5 years	None
Cranial MRI ± spinal MRI if initially positive for infants and patients not eligible to radiotherapy	Every 3 months	Every 4 months	Every 6 months	Every 12 months
Full blood test	At 1 year	Once per year	Once per year	None

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APPENDIX 1 – ABBREVIATIONS

ALT: Alanine Aminotransferase

ARAC: Aracytin

AST: Aspartate Aminotransferase

CBDCA: Carboplatin

CDDP: Cisplatin

CNS: Central nervous system

CSF: Cerebrospinal fluid

CSI: Craniospinal irradiation

CT: Computed tomography

CY: Cyclophosphamide

EFS: Event-free survival

EMA: Epithelial membrane antigen

FLAIR: Fluid-Attenuated Inversion Recovery

GFAP: Glial fibrillary acidic protein

GGT: Gamma-Glutamyl Transferase

HD: High dose

HDAC: Histone deacetylase

HDACi: Histone deacetylase inhibitors

HFRT: Hypofractionated radiation therapy

HIV: human immunodeficiency virus

IFO: Ifosfamide

ITMTX: Intrathecal methotrexate

LDH: Lactate dehydrogenase

MRI: Magnetic Resonance Imaging

MTX: Methotrexate

NF2: Neurofibromatosis type 2

OS: Overall survival

PBSC: Peripheral blood stem cell rescue

PBT: proton beam therapy

PCB: Procarbazine

PD: Progression disease

R: Randomisation

RD: Residual disease

RT: Radiotherapy

TTT: Thiotepa

VBL: Vinblastine

VCR: Vincristine

VP16: Etoposide

WHO: World Health Organization

APPENDIX 2 – CHEMOTHERAPY ADMINISTRATION

Table VII: VEC course

Cycle 1 Week 1 Day 1-3	D1: VCR: 1.5mg/m^2 (max 2mg) as an IV bolus D1-D3: VP16:100mg/m^2 infused over 1-4hours D1: CY: 3000mg/m^2 in 3 divided infusions (1000mg/m^2/dose) infused over 60 minutes at 8 hourly intervals.
Cycle 2	D22: VCR: 1.5mg/m^2 (max 2mg) as an IV bolus D22-24: VP16: 100mg/m^2 infused over 1-4hours

Week 4 Days 22-24	D22: CY: 3000mg/m^2 in 3 divided infusions (1000mg/m^2/dose) infused over 60 minutes at 8 hourly intervals.
Cycle 3 Week 7 Days 43-45	D1: VCR: 1.5mg/m^2 (max 2mg) as an IV bolus D1-D3: VP16:100mg/m^2 infused over 1-4hours D1: CY: 3000mg/m^2 in 3 divided infusions (1000mg/m^2/dose) infused over 60 minutes at 8 hourly intervals.

The body surface area must be capped at 2.00 m^2 for any calculation of the IMP dose to be administered.
For babies weighing less than 10 kg, doses will be based on body weight (BW) rather than body
surface area (BSA). The following doses should be used:
· VCR: 0.05 mg/kg as an i.v. bolus
· VP16: 3.3 mg/kg infused over 1 – 4 hours according to standard institutional practice.
· CY: 100mg/kg in 3 divided infusions (33mg/kg/infusion) infused over 60 minutes at eight hourly intervals.

Table VIII: UKCCSG/SIOP CNS 9204

Cycle nº	1	2	3	4	5	6	7
VCR-CBDCA	D1	D57	D113	D169	D225	D281	D337
VCR-MTX	D15	D71	D127	D183	D239	D295	D351
VCR-CY	D29	D85	D141	D197	D253	D309	D365
CDDP 2-days infusion	D43 44	D99 100	D154 155	D211 212	D267 268	D323 324	D379 380

	Dose > 1 year or > 10kg	**Dose for infants 6months to 1 year or ≤ 10kg**	**Dose for infants < 6months**
VCR	1.5mg/m^2 x 1	1.125mg/m^2 x 1	0.75mg/m^2 x 1
CBDCA	550mg/m^2 x 1	412.5mg/m^2 x 1	275mg/m^2 x 1
MTX	8000mg/m^2 x 1	6000mg/m^2 x 1	4000mg/m^2 x 1
CY	1500mg/m^2 x 1	1125mg/m^2 x 1	750mg/m^2 x 1
CDDP	40mg/m^2 x 2	30mg/m^2 x 2	20mg/m^2 x 2
Valproate	30mg/kg/day	30mg/kg/day	30mg/kg/day

HIT-SKK/and modified HIT-SKK

- **Table IX: SKK- Cyclophosphamide/Vincristine**:

Day	Drug	Dose	Route
1	CY	800mg/m^2/day	1 hour IV
	VCR	1.5mg/m^2 (max 2mg)	IV bolus
2	CY	800mg/m^2/day	1 hour IV
3	CY	800mg/m^2/day	1 hour IV
15	Continue with next block		

Age specific dose reductions are required for CY and VCR. < 6 months: ⅔ of the m² dosage 7 to 12 month age: ⅘ of the m² dosage >12 month: full m² dosage. Intraventricular MTX dose is 1 mg/day in children < 6 months.

- **Table X: SKK - high-dose Methotrexate /Vincristine:**

Day	Drug	Dose	Route
1	MTX	5g/m^2 divided in 2 doses: 0,5g/m^2 4,5g/m^2	 0,5 hour IV 23,5 hours IV
	VCR	1.5mg/m^2 (max 2mg)	IV bolus
2	Leucovorin rescue	15mg/m^2 x 6 q6 hours	IV start h42
15	Continue with next block		

Age specific dose reduction is required for VCR. < 6 months: 2/3 of the m² dosage 7 to 12 months age: 4/5 of the m² dosage >12 month: full m² dosage Intraventricular MTX dose is 1 mg/day in children < 6 months.

- **Table XI: SKK - Carboplatin/Etoposide:**

Day	Drug	Dose	Route
1	CBDCA	200mg/m^2/day	1 hour IV
	VP16	150mg/m^2/day	30 min IV
2	CBDCA	200mg/m^2/day	1 hour IV
	VP16	150mg/m^2/day	30 min IV
3	CBDCA	200mg/m^2/day	1 hour IV
	VP16	150mg/m^2/day	30 min IV

Age specific dose reduction is required for CBDCA and may be considered for VP16. 12 months: full m² dosage Intraventricular MTX dose is 1 mg/day in children < 6 months.