Surveillance imaging for high-grade childhood brain tumors: what to do ten years after completion of treatment?

M Otth¹, K Scheinemann^{2, 3, 4}

¹ Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

² Division of Hematology/ Oncology, University Children's Hospital beider Basel (UKBB) and University of Basel, Switzerland

³ Division of Hematology/ Oncology; McMaster Children's Hospital and McMaster University Hamilton Canada

⁴ Division of Hematology/ Oncology; Hospital for children and adolescents, Kantonsspital Aarau, Switzerland

Corresponding author:

Maria Otth, University of Bern, Institute of Social and Preventive Medicine (ISPM), Mittelstrasse 43, 3012 Bern, Switzerland

Phone: +0041 31 631 56 70

Mail: maria.otth@ispm.unibe.ch

23 Abstract word count: 85

24 Text word count: 2553

25 Number of tables: 2

26 Number of figures: 0

27 Number of supplemental files: 0

28

29 Short running title: Surveillance imaging in high-grade childhood CNS tumors

30

31

32 Keywords: high-grade, brain tumor, childhood, surveillance imaging

33

34

35 Abbreviation key

ATRT	Atypical teratoid rhabdoid tumor
CNS	Central nervous system
DIPG	Diffuse intrinsic pons glioma
EPN	Ependymoma
FA	Fractional anisotropy
FLAIR	Fluid attenuation inversion recovery
GBM	Glioblastoma multiforme
GTR	Gross total resection
HGG	High-grade glioma
IVM	Intracerebral vascular malformations
LGG	Low-grade glioma
MB	Medulloblastoma
MRI	Magnetic resonance imaging
PBL	Pineoblastoma
PNET	Primitive neuroectodermal tumor
SMN	Secondary malignant neoplasm
stPNET	Supratentorial primitive neuroectodermal tumor
WML	White matter lesion

36

37

Abstract

Brain tumors are the second most common childhood cancer. Treatment protocols for high-grade pediatric brain tumors recommend regular follow-up imaging for up to ten years. We review maximal time to recurrence and minimal time to radiologically detectable long-term sequelae like secondary malignancies, vascular complications and white matter disease. No tumors recurred after the ten-year point, but radiological long-term sequelae grew more common as the treatment completion date receded. We do not recommend regular imaging more than ten years after treatment has ended, unless there are clinical symptoms.

Introduction

Tumors of the central nervous system (CNS) are the second most common tumor in childhood after leukemia. The incidence is comparable in western countries (5.47/100,000 aged 0-14 years and 5.67/100,000 aged 0-19 years in the US, 2-4/100,000 aged 0-15 years in Germany and Switzerland)^{1,2}. Advances in imaging techniques, neurosurgery, radiotherapy, chemotherapy and supportive care have increased the survival rate significantly. Five-year relative survival for all brain tumors has increased from around 60% at the end of the 1970s to around 72.5% by 2007-2013³, though the survival rate varies between different pediatric CNS tumors. When they are cured of their primary malignancy, children need regular follow-up investigations and screenings for tumor recurrence and long-term side effects caused by chemotherapy, radiotherapy, surgery or the tumor itself. For most tumors, a national and/or international treatment protocol recommends procedures for initial diagnosis, treatment and follow up, but these recommendations usually cover only the first five or ten years after the end of treatment.

This review summarizes the most important findings detectable on imaging ten years or more after the end of treatment for pediatric high-grade brain tumors, which includes the period of possible tumor recurrence. We also summarize possible long-term sequelae visible on imaging (secondary malignant neoplasm, vascular complications, and white matter disease) caused by the treatment.

Methods

We used PubMed for the literature search. Search terms included the different biological types of high-grade brain tumors (medulloblastoma [MB], ependymoma [EPN], supratentorial primitive

neuroectodermal tumor [stPNET], atypical teratoid rhabdoid tumor [ATRT], malignant glioma/high grade glioma [HGG] and diffuse intrinsic pons glioma [DIPG]) and the term “embryonal tumors”. In addition to the single biological subtypes we combined those with the terms “surveillance imaging”, “relapse”, “relapse pattern”, “outcome”, “cavernoma”, “intracerebral cavernous malformations”, “intracerebral vascular malformations” (IVM), “secondary malignant neoplasm (SMN)”, “secondary malignancy”, “leukomalacia”, “leukoencephalopathy”, “white matter” and “childhood”. We also screened the reference lists of the eligible publications.

Inclusion criteria for all publications are diagnosis of a high-grade brain tumor and age at first tumor diagnosis of 0-18 years. We also included publications with patient aged >18 years if the proportion of the pediatric population was described separately. An additional inclusion criterion for tumor recurrence was diagnosis after 1999; these studies have comparable and less heterogeneous treatment modalities, especially for radiotherapy. We only evaluated time to first recurrence. Secondary malignant neoplasm, intracerebral vascular malformation, and leukoencephalopathy have separate inclusion criteria for the year of first tumor diagnosis (after 1989) and year of publication (after 1999).

We excluded all publications with less than 10 patients and those where leukoencephalopathy developed during the treatment. Patients with tumor predisposition syndrome are excluded, as in this population follow-up recommendations are more complex and have to include multiple different tumor types also outside of the CNS.

Results

Tumor recurrence

Table 1 provides an overview of the most important findings from the eligible studies on tumor recurrence.

Medulloblastoma (MB)

Medulloblastoma make up 15-30% of all brain tumors and are the second most common brain tumor after astrocytoma⁴. Around 50% develop before the age of 5 years. Initial metastatic disease is present in about one third^{5,6}.

Tumor recurrence rate was between 18.7%-40%.^{5,7-14}. No relapse occurred more than ten years after diagnosis. The longest documented latency period was 7.9 years, in a patient with standard risk MB⁷. The proportion of late relapse, arbitrarily defined as >5 years from diagnosis, is mentioned in two publications and is 8% and 7% respectively^{7,8}. According to Sabel et al. and Perreault et al. 69% and 46% of all recurrences were asymptomatic and detected by surveillance MRI^{7,9,10}.

Ependymoma (EPN)

EPN represent 10 % of all CNS tumors in childhood. They occur mostly in the first decade of life and more than 50% of children are aged <5 years at diagnosis. EPN present with initial leptomeningeal dissemination in 5-10% of cases^{4,15,16}.

30 – 54% of patients relapsed between 1 month and 8.6 years from diagnosis, with a mean of 12 to 19 months^{9,17-20}. No data concerning symptomatic or asymptomatic recurrence are available.

Atypical teratoid rhabdoid tumor (ATRT)

ATRT are rare (1-2%) brain tumor in childhood and affect predominantly infants and toddlers. About two-third of newly diagnosed ATRT occur before the age of 3 years. In 21-30%, dissemination is present at initial diagnosis²¹⁻²³. Relapse occur in 40 – 74% of patients with a mean latency period around 5 month and the latest relapse after 3.2 years^{9,24-28}. No data concerning symptomatic or asymptomatic recurrence are available.

Central nervous system primitive neuroectodermal tumors (CNS-PNET), Pineoblastoma (PBL) CNS-PNET and PBL represent 2.5% - 4.8% and 0.6% of all CNS tumors respectively^{4,29}. In the reviewed literature, initial metastatic disease was present 35% and 48% respectively^{10,30}. The rate of recurrence was between 42% and 76%^{10,30,31}. The latest manifestation occurred after 4.5 years in a patient with CNS-PNET¹⁰. No data concerning symptomatic or asymptomatic recurrence available.

High-grade glioma (HGG) and Diffuse intrinsic pons glioma (DIPG) HGG together with DIPG represent 8 - 17% of all CNS tumors in childhood and adolescence up to 19 years of age and are responsible for a relevant part of mortality (up to 40% of all brain tumors)^{4,32,33}. According to data from four consecutive German HGG protocols, about 3% have initial metastatic disease³⁴. The rate of progressive disease after one year was 75% in the study from Macy et al³⁵. The event free-survival after one year was higher (43%) according to Wolff et al³⁶. The 5-year event-free survival in this cohort was 13%.

Radiological long-term sequelae

Table 2 summarizes the most important findings from the eligible studies on SMN, IVM and WML.

Secondary malignant neoplasia

The median follow-up from diagnosis for the six eligible studies ranges from 1.0 to 10.0 years with a maximum of 15.0 years^{7,11,37-40}. The primary diagnosis was either medulloblastoma, ependymoma or HGG/DIPG. All SMN occurred in patients after radiotherapy. Secondary brain tumors were detected in 0.1 – 4.1% of former brain tumor patients. The histology of all 19 cerebral SMN are available^{7,11,37-40}. Hereof 79% are high-grade lesions (high-grade glioma and PNET), 15% are meningioma, and 5% are pilocytic astrocytoma. Time to detection of SMN is available from five studies, ranging from 2.4 years (PNET) to 10.3 years (high-grade glioma)^{7,11,37-39}. Time to detection of low-grade tumors is available in two cases and is 6.5 years (pilocytic astrocytoma) and 10.2 years (meningioma) respectively^{37,39}. In case of high-grade tumors (n=11) time ranges from 2.4 to 10.3 years.

Intracerebral vascular malformations

Only one study assessing radiation-induced cavernoma in medulloblastoma patients fulfilled the inclusion criteria⁴¹. During the observation period of mean 7.2 years, 31% developed at least one intracerebral cavernoma. The cumulative incidence rate was 5.6%, 14% and 43% 3, 5 and 10 years following radiotherapy for MB. Time to detection of a vascular malformation lied between 1.1 and 16.1 years with a median of 6.6 years. One out of 18 patients had clinical symptoms at

diagnosis. He presented five years after treatment with seizure, headache, and emesis. All patients received radiotherapy to the brain.

Leukoencephalopathy/ White matter lesions

WML is a well-known late effect after treatment for pediatric brain tumors, either after focal irradiation or after low dose craniospinal radiotherapy and chemotherapy^{42,43}. Depending on the severity, mostly studies classify WML in grade 1-3, rarely up to grade 4. Grade 1 lesions correspond to small areas with high signal in T2* and FLAIR in MRI. These lesions increase in grade 2 and become cystic or hemorrhagic in grade 3 and 4 lesions⁴⁴. These changes can occur in parallel with an increase in subarachnoidal space and ventriculomegaly⁴³. Different grades of WML can manifest in the same patient⁴²⁻⁴⁵. The incidence of WML lies between 33% and 100%⁴²⁻⁴⁶. Two studies included MB only^{42,45,46}; the remaining two include more than one biological type of brain tumor^{43,44}. All patients received different combinations of chemotherapy and radiotherapy. The percentage of grade 1 lesions in each study ranges from 33 to 66%. Grade II lesions and grade III lesions were visible in 7-33% and 29% respectively.

Discussion

We found no recurrence of the primary brain tumor, either local or distant, ten years or more after the end of treatment in the reviewed literature^{5,7-14,18-20,24-28,30,31,35,36,47,48}. After combining the latency period from all relapses, median time to relapse was 13.7 months; average minimal latency times were 3.3 months and a maximum of 49.0 months. A patient diagnosed with ependymoma had the longest latency period (103 months). Overall, these results do not seem to

justify routine screening to detect tumor recurrence more than ten years after the end of treatment.

Radiotherapy is a known risk factor for developing SMN in the previously irradiated field. Data from the large Childhood Cancer Survivor Study (CCSS) show that the risk for SMN in the brain increases as the diagnosis recedes. Results from large studies emphasise a linear dose-response-relationship between meningioma and glioma as SMN with a steady increase of occurrence for both tumors over time (cumulative incidence 3.3% at 25 years; 3.5% at 30 years)^{49,50}. Most of the SMN in the reviewed literature are high-grade tumors. Only two studies reported occurrence of secondary meningioma^{37,40}. Studies with longer follow-up periods show a larger proportion of secondary meningioma. In the CCSS cohort, the cumulative incidence of benign meningioma was 3.3% after a median follow-up of 19.6 years⁵¹. The latency period for SMN in the brain is very heterogeneous in the reviewed literature (2.4 to 10.3 years) and the development of SMN follows no predictable pattern. For slowly growing tumors (e.g. meningioma), the prognosis is not inferior if the tumor is diagnosed due to clinical symptoms compared to earlier detection by surveillance MRI. Data of women with newly diagnosed meningioma during pregnancy support this suggestion⁵²⁻⁵⁴. In case of absent neurological symptoms or deterioration, the management provides tight follow-up and surgery after delivery. The interval between diagnosis and surgery can thereby last up to several weeks⁵²⁻⁵⁴. To detect fast-growing secondary brain tumors (e.g. GBM) in an early stage, the interval between the scans would have to be very short. Even though the possibility is high to miss the tumor on MRI because the tumor was not visible on the previous but manifests clinically before the subsequent examination. In summary, it is not possible to recommend regular screening for early detection of SMN.

Cavernoma occur more often in previously irradiated patients and detection rate depends on imaging techniques. The prevalence of cavernoma in the reviewed study is 31%. This prevalence is higher than in non-irradiated children and young adults with a prevalence of 0.6%⁵⁵ and also higher than in other publications including patients partially diagnosed before 1990 with rates of 3.4% and 4.2%^{56,57}. Different MRI techniques could cause some of these differences. In the study from Burn et al. no T2*-weighted imaging was performed⁵⁶. This technique is sensitive to detect blood artefacts and was used in the reviewed study. Studies including patients from past eras, not using specific MR techniques, probably underestimate the prevalence of cavernoma. Cavernoma bear the risk of spontaneous bleeding. In the study from Lew et al. 20 lesions were longitudinally followed⁴¹. They increased in size in 70% of cases, were stable in 15%, and a decreased in 15%. Despite an increase in size in 70% of cases, no patient suffered from acute bleeding during the follow-up period. The hemorrhage rate in non-irradiated children is 3.3% and 1.6% per patient-year respectively^{55,58}. Other publications show a bleeding rate for radiation-induced cavernoma of 10%⁵⁹. Radiation dose and time of follow-up may have an effect on the development of cavernoma. Unfortunately, the reviewed study did not comment on the possible effect of radiation dose. Cutsforth et al. showed, that patients treated with higher radiation doses had a shorter period to detection of cavernoma⁵⁹. Burn et al. showed no correlation between radiation dose and the latency period⁵⁶. According to Lew et al. with increasing time from end of treatment, the cumulative incidence of cavernoma increases⁴¹. With the knowledge of the dynamic behaviour in the natural course of cavernoma, we recommend a wait-and-see strategy with close follow-up imaging in case of an asymptomatic incidental finding. Due to the wide

range of latency period to detection of cavernoma, no interval for regular follow-up imaging can be deduced.

A second cerebral vascular disorder observed after radiotherapy to the brain is moyamoya. Most studies evaluating moyamoya after radiotherapy include to a large proportion patients with neurofibromatosis 1 (NF1), a tumor predisposition syndrome. These patients are at increased risk for moyamoya independent of radiotherapy and separate guidelines for surveillance imaging exist. After excluding these patients from otherwise eligible studies, the number of patients without moyamoya is far less than $10^{60,61}$. Both studies showed that radiation to the circle of Willis or the supratentorial region is a risk factor for moyamoya. In the study from Ullrich et al., the high rate of optic pathway glioma and therefore patients with probably having NF1 might bias this observation. In the population of Wu et al., only 25% suffered from optic pathway glioma, but all received suprasellar radiotherapy. Therefore, suprasellar radiotherapy seems to be a risk factor for moyamoya.

Most WML in the reviewed literature are grade 1. In the cohort from Dietrich et al., no child with WML suffered from neurological deficits, but specific neuropsychological testing was not performed. In three studies, imaging by conventional MRI was completed by the measurement of white matter anisotropy, performed by fractional anisotropy (FA) ^{42,45,46}. Results show a relevant reduction of FA in selected parts of the brain in previously irradiated children compared to non-irradiated brains. There seems to be a correlation between FA-reduction and younger age at radiotherapy as well as a time span of more than 5 years after radiation. A reduced FA or white matter integrity shows a correlation with lower cognitive outcome and executive functions^{42,46}. It seems that special imaging modalities (e.g. diffusion weighted imaging, measurement of

anisotropy) are more sensitive in detection of white matter lesions than T2 weighted images alone⁴². The consequences of detected WML of any grade and the implications for therapeutic interventions are the focus of current research. We assume that early intervention, already preventive, with specific neuropsychological training help these patients to prevent the development or progression of impaired cognitive and executive functions.

The small number of studies that were eligible after we applied strict inclusion criteria, especially the limits imposed by year of diagnosis and the requirement for at least 10 patients limited our review. Since diagnoses were 1990 and onwards, the follow-up period was short, which probably biases the distribution towards more high-grade SMN and underestimates the rate of low-grade SMN. The large differences in cumulative incidence rate of vascular malformations we identified is most likely a result of small sample sizes and imaging techniques. Patients have been treated with newer modalities, so our results apply to survivors now entering follow-up care.

If a patient has strong new headache or neurological symptoms 10 years or more after treatment for a high-grade brain tumor, we recommend prompt imaging, including appropriate sequences for vascular diseases. If imaging reveals a cavernoma in a critical region, we recommend regular follow-up imaging⁶². We do not recommend surveillance imaging for small cavernoma in non-critical regions⁴¹.

We found that screening imaging more than 10 years after completing treatment for childhood high-grade brain tumors is not indicated in absence of clinical symptoms because tumors do not

recur after such a long period of time, and long-term sequelae (SMN, IVM, WML) occur in such a broad time spectrum that no reasonable interval for screening imaging can be defined.

Conflict of Interest Statement

There is no conflict of interest

Acknowledgements

References

1. Chambal L, Gudo ES, Carimo A, et al. HBV infection in untreated HIV-infected Adults in Maputo, Mozambique. *Open Forum Infectious Diseases*. 2017;4:S657.
2. SCCR. Annual_Report_SCCR_2015_2016. 2016;
https://www.kinderkrebsregister.ch/fileadmin/KKR08/uploads/pdf/Jahresberichte/Annual_Report_SCCR_2015_2016_Einzel_web.pdf.
3. Coetzee J, Hunt G, Jaffer M, et al. HIV-1 viraemia and drug resistance amongst female sex workers in Soweto, South Africa: A cross sectional study. *PLoS One*. 2017;12(12):e0188606.
4. Kaatsch P, Rickert CH, Kuhl J, Schuz J, Michaelis J. Population-based epidemiologic data on brain tumors in German children. *Cancer*. 2001;92(12):3155-3164.
5. von Bueren AO, von Hoff K, Pietsch T, et al. Treatment of young children with localized medulloblastoma by chemotherapy alone: results of the prospective, multicenter trial HIT 2000 confirming the prognostic impact of histology. *Neuro-oncology*. 2011;13(6):669-679.
6. Scheinemann K BE. *Pediatric neuro-oncology*. Springer New York; 2015. 127 p.
7. Sabel M, Fleischhack G, Tippelt S, et al. Relapse patterns and outcome after relapse in standard risk medulloblastoma: a report from the HIT-SIOP-PNET4 study. *Journal of neuro-oncology*. 2016;129(3):515-524.
8. Koschmann C, Bloom K, Upadhyaya S, Geyer JR, Leary SE. Survival After Relapse of Medulloblastoma. *Journal of pediatric hematology/oncology*. 2016;38(4):269-273.
9. Perreault S, Lober RM, Carret AS, et al. Surveillance imaging in children with malignant CNS tumors: low yield of spine MRI. *Journal of neuro-oncology*. 2014;116(3):617-623.
10. Perreault S, Lober RM, Carret AS, et al. Relapse patterns in pediatric embryonal central nervous system tumors. *Journal of neuro-oncology*. 2013;115(2):209-215.
11. Dufour C, Kieffer V, Varlet P, et al. Tandem high-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk medulloblastoma or supratentorial primitive neuro-ectodermic tumors. *Pediatric blood & cancer*. 2014;61(8):1398-1402.

- 317 12. Odagiri K, Omura M, Hata M, et al. Treatment outcomes and late toxicities in patients with
318 embryonal central nervous system tumors. *Radiation oncology (London, England)*. 2014;9:201.
- 319 13. Sung KW, Lim DH, Son MH, et al. Reduced-dose craniospinal radiotherapy followed by tandem
320 high-dose chemotherapy and autologous stem cell transplantation in patients with high-risk
321 medulloblastoma. *Neuro-oncology*. 2013;15(3):352-359.
- 322 14. von Bueren AO, Kortmann RD, von Hoff K, et al. Treatment of Children and Adolescents With
323 Metastatic Medulloblastoma and Prognostic Relevance of Clinical and Biologic Parameters.
324 *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*.
325 2016;34(34):4151-4160.
- 326 15. Cage TA, Clark AJ, Aranda D, et al. A systematic review of treatment outcomes in pediatric
327 patients with intracranial ependymomas. *Journal of neurosurgery Pediatrics*. 2013;11(6):673-
328 681.
- 329 16. Scheinemann K BE. *Pediatric neuro-oncology*. Springer New York; 2015. 139 p.
- 330 17. Venkatramani R, Dhall G, Patel M, et al. Supratentorial ependymoma in children: to observe or
331 to treat following gross total resection? *Pediatric blood & cancer*. 2012;58(3):380-383.
- 332 18. Massimino M, Miceli R, Giangaspero F, et al. Final results of the second prospective AIEOP
333 protocol for pediatric intracranial ependymoma. *Neuro-oncology*. 2016;18(10):1451-1460.
- 334 19. Sato M, Gunther JR, Mahajan A, et al. Progression-free survival of children with localized
335 ependymoma treated with intensity-modulated radiation therapy or proton-beam radiation
336 therapy. *Cancer*. 2017;123(13):2570-2578.
- 337 20. Tensaouti F, Ducassou A, Chaltiel L, et al. Patterns of failure after radiotherapy for pediatric
338 patients with intracranial ependymoma. *Radiotherapy and oncology : journal of the European
339 Society for Therapeutic Radiology and Oncology*. 2017;122(3):362-367.
- 340 21. Hilden JM, Meerbaum S, Burger P, et al. Central nervous system atypical teratoid/rhabdoid
341 tumor: results of therapy in children enrolled in a registry. *Journal of clinical oncology : official
342 journal of the American Society of Clinical Oncology*. 2004;22(14):2877-2884.
- 343 22. Lafay-Cousin L, Hawkins C, Carret AS, et al. Central nervous system atypical teratoid rhabdoid
344 tumours: the Canadian Paediatric Brain Tumour Consortium experience. *European journal of
345 cancer (Oxford, England : 1990)*. 2012;48(3):353-359.
- 346 23. Scheinemann K BE. *Pediatric neuro-oncology*. Springer New York; 2015. 164 p.
- 347 24. Bartelheim K, Nemes K, Seeringer A, et al. Improved 6-year overall survival in AT/RT - results of
348 the registry study Rhabdoid 2007. *Cancer medicine*. 2016;5(8):1765-1775.
- 349 25. Benesch M, Bartelheim K, Fleischhack G, et al. High-dose chemotherapy (HDCT) with auto-SCT in
350 children with atypical teratoid/rhabdoid tumors (AT/RT): a report from the European Rhabdoid
351 Registry (EU-RHAB). *Bone marrow transplantation*. 2014;49(3):370-375.
- 352 26. Chi SN, Zimmerman MA, Yao X, et al. Intensive multimodality treatment for children with newly
353 diagnosed CNS atypical teratoid rhabdoid tumor. *Journal of clinical oncology : official journal of
354 the American Society of Clinical Oncology*. 2009;27(3):385-389.
- 355 27. Sung KW, Lim DH, Yi ES, et al. Tandem High-Dose Chemotherapy and Autologous Stem Cell
356 Transplantation for Atypical Teratoid/Rhabdoid Tumor. *Cancer research and treatment : official
357 journal of Korean Cancer Association*. 2016;48(4):1408-1419.
- 358 28. Zaky W, Dhall G, Ji L, et al. Intensive induction chemotherapy followed by myeloablative
359 chemotherapy with autologous hematopoietic progenitor cell rescue for young children newly-
360 diagnosed with central nervous system atypical teratoid/rhabdoid tumors: the Head Start III
361 experience. *Pediatric blood & cancer*. 2014;61(1):95-101.
- 362 29. Scheinemann K BE. *Pediatric neuro-oncology*. Springer New York; 2015. 134 p.

30. Friedrich C, von Bueren AO, von Hoff K, et al. Treatment of young children with CNS-primitive neuroectodermal tumors/pineoblastomas in the prospective multicenter trial HIT 2000 using different chemotherapy regimens and radiotherapy. *Neuro-oncology*. 2013;15(2):224-234.
31. Gerber NU, von Hoff K, Resch A, et al. Treatment of children with central nervous system primitive neuroectodermal tumors/pinealoblastomas in the prospective multicentric trial HIT 2000 using hyperfractionated radiation therapy followed by maintenance chemotherapy. *International journal of radiation oncology, biology, physics*. 2014;89(4):863-871.
32. Ostrom QT, Gittleman H, Xu J, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009-2013. *Neuro-oncology*. 2016;18(suppl_5):v1-v75.
33. Scheinemann K BE. *Pediatric neuro-oncology*. Springer New York; 2015. 101 p.
34. Benesch M, Wagner S, Berthold F, Wolff JE. Primary dissemination of high-grade gliomas in children: experiences from four studies of the Pediatric Oncology and Hematology Society of the German Language Group (GPOH). *Journal of neuro-oncology*. 2005;72(2):179-183.
35. Macy ME, Kieran MW, Chi SN, et al. A pediatric trial of radiation/cetuximab followed by irinotecan/cetuximab in newly diagnosed diffuse pontine gliomas and high-grade astrocytomas: A Pediatric Oncology Experimental Therapeutics Investigators' Consortium study. *Pediatric blood & cancer*. 2017;64(11).
36. Wolff JE, Kortmann RD, Wolff B, et al. High dose methotrexate for pediatric high grade glioma: results of the HIT-GBM-D pilot study. *Journal of neuro-oncology*. 2011;102(3):433-442.
37. Karremann M, Hoffmann M, Benesch M, Kwiecien R, von Bueren AO, Kramm CM. Secondary Solid Malignancies After High-Grade Glioma Treatment in Pediatric Patients. *Pediatric hematology and oncology*. 2015;32(7):467-473.
38. Massimino M, Gandola L, Barra S, et al. Infant ependymoma in a 10-year AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) experience with omitted or deferred radiotherapy. *International journal of radiation oncology, biology, physics*. 2011;80(3):807-814.
39. Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. *Neuro-oncology*. 2013;15(1):97-103.
40. von Hoff K, Hinkes B, Gerber NU, et al. Long-term outcome and clinical prognostic factors in children with medulloblastoma treated in the prospective randomised multicentre trial HIT'91. *European journal of cancer (Oxford, England : 1990)*. 2009;45(7):1209-1217.
41. Lew SM, Morgan JN, Psaty E, Lefton DR, Allen JC, Abbott R. Cumulative incidence of radiation-induced cavernomas in long-term survivors of medulloblastoma. *Journal of neurosurgery*. 2006;104(2 Suppl):103-107.
42. Khong PL, Kwong DL, Chan GC, Sham JS, Chan FL, Ooi GC. Diffusion-tensor imaging for the detection and quantification of treatment-induced white matter injury in children with medulloblastoma: a pilot study. *AJNR American journal of neuroradiology*. 2003;24(4):734-740.
43. Kellie SJ, Chaku J, Lockwood LR, O'Regan P, Waters KD, Wong CK. Late magnetic resonance imaging features of leukoencephalopathy in children with central nervous system tumours following high-dose methotrexate and neuraxis radiation therapy. *European journal of cancer (Oxford, England : 1990)*. 2005;41(11):1588-1596.
44. Dietrich U, Wanke I, Mueller T, et al. White matter disease in children treated for malignant brain tumors. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery*. 2001;17(12):731-738.
45. Rueckriegel SM, Driever PH, Blankenburg F, Ludemann L, Henze G, Bruhn H. Differences in supratentorial damage of white matter in pediatric survivors of posterior fossa tumors with and

- without adjuvant treatment as detected by magnetic resonance diffusion tensor imaging. *International journal of radiation oncology, biology, physics*. 2010;76(3):859-866.
46. Brinkman TM, Reddick WE, Luxton J, et al. Cerebral white matter integrity and executive function in adult survivors of childhood medulloblastoma. *Neuro-oncology*. 2012;14 Suppl 4:iv25-36.
47. Rootman MS, Konen O, Fried I, Toledano H. Preferential sites of metastatic relapse on MRI of initially localized ependymoma in children. *Clinical imaging*. 2017;44:12-15.
48. Venkatramani R, Ji L, Lasky J, et al. Outcome of infants and young children with newly diagnosed ependymoma treated on the "Head Start" III prospective clinical trial. *Journal of neuro-oncology*. 2013;113(2):285-291.
49. Armstrong GT. Long-term survivors of childhood central nervous system malignancies: the experience of the Childhood Cancer Survivor Study. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2010;14(4):298-303.
50. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Journal of the National Cancer Institute*. 2006;98(21):1528-1537.
51. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *Journal of the National Cancer Institute*. 2009;101(13):946-958.
52. Laviv Y, Bayoumi A, Mahadevan A, Young B, Boone M, Kasper EM. Meningiomas in pregnancy: timing of surgery and clinical outcomes as observed in 104 cases and establishment of a best management strategy. *Acta neurochirurgica*. 2017.
53. Kanaan I, Jallu A, Kanaan H. Management Strategy for Meningioma in Pregnancy: A Clinical Study. *Skull base : official journal of North American Skull Base Society [et al]*. 2003;13(4):197-203.
54. Constantin Dumitrescu B GTL, Radu Gorgan M. Pregnant woman with an intracranial meningioma – case report and review of the literature. *Romanian Neurosurg*. 2014.
55. Al-Holou WN, O'Lynnger TM, Pandey AS, et al. Natural history and imaging prevalence of cavernous malformations in children and young adults. *Journal of neurosurgery Pediatrics*. 2012;9(2):198-205.
56. Burn S, Gunny R, Phipps K, Gaze M, Hayward R. Incidence of cavernoma development in children after radiotherapy for brain tumors. *Journal of neurosurgery*. 2007;106(5 Suppl):379-383.
57. Gastelum E, Sear K, Hills N, et al. Rates and characteristics of radiographically detected intracerebral cavernous malformations after cranial radiation therapy in pediatric cancer patients. *Journal of child neurology*. 2015;30(7):842-849.
58. Gross BA, Du R, Orbach DB, Scott RM, Smith ER. The natural history of cerebral cavernous malformations in children. *Journal of neurosurgery Pediatrics*. 2015:1-6.
59. Cutsforth-Gregory JK, Lanzino G, Link MJ, Brown RD, Jr., Flemming KD. Characterization of radiation-induced cavernous malformations and comparison with a nonradiation cavernous malformation cohort. *Journal of neurosurgery*. 2015;122(5):1214-1222.
60. Ullrich NJ, Robertson R, Kinnamon DD, et al. Moyamoya following cranial irradiation for primary brain tumors in children. *Neurology*. 2007;68(12):932-938.
61. Wu YH, Chang FC, Liang ML, et al. Incidence and long-term outcome of postradiotherapy moyamoya syndrome in pediatric patients with primary brain tumors: a single institute experience in Taiwan. *Cancer medicine*. 2016;5(8):2155-2160.
62. Lee JW, Kim DS, Shim KW, et al. Management of intracranial cavernous malformation in pediatric patients. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery*. 2008;24(3):321-327.

TABLE 1 Overview of the most important findings from the eligible studies on tumor recurrence

Study/ Year	Trial type Year of diagnosis FU, y, median	Number of patients	Number of relapse % (n)	Latency from primary diagnosis to relapse, mo, median
Medulloblastoma				
Dufour et al, 2014 ¹¹	Single center, prospective 2001 - 2010 FU: 0.8 – 11.3 (4.4)	21	28.5% (6)	9.2 – 74.4 (19.5)
Koschmann et al, 2016 ⁸	Single center, retrospective 2000 - 2010 FU: 3.6 – 62.6 (18.0)	47	29.8 % (14)	3.6 – 62.6 (18.0)
Odagiri et al, 2014 ¹²	Single center, retrospective 2003 - 2011 FU: 1.9 – 9.1 (6.5)	16	18.7% (3)	n.a.
Perreault et al, 2013 and 2014 ^{9,10}	Two centers, retrospective 2000 – 2011 FU: 0.23 – 11.8 (4.3)	89	29.2% (26)	0.5 – 76 (16)
Sabel et al, 2016 ⁷	Multicenter, prospective 2001 - 2006 FU: (7.8)	338	21% (72)	2 - 95 (26)
Sung et al, 2013 ¹³	Single center, prospective 2005 - 2010 FU: 1.9 – 6.8 (3.8)	20	20% (4)	6 – 21
Von Bueren at al, 2011 ⁵	Multicenter, prospective 2001 - 2005 FU: 1.3 – 8.2 (4.5)	45	40% (18)	2.4 – 53.9 (15.6)
Von Bueren et al, 2016 ¹⁴	Multicenter, prospective 2001 – 2007 FU: 1.2 – 9.5 (5.4)	123	38.2% (47)	SHH group: 9.6 – 16.8 (12.8) Group 3: 1.2 – 38.4 (9.6) Group 4: 4.8 – 92.4 (32.4)

Ependymoma				
Massimio et al, 2016 ¹⁸	Multicenter, prospective 2002 - 2014 FU: 3.4 – 9.1 (5.6)	160	30.6% (49)	4 – 103 (19)
Perreault et al, 2014 ⁹	Two centers, retrospective 2000 – 2011 FU: 0.5 – 11.1 (3.9)	52	50% (26)	1 – 65 (16)
Rootman et al, 2017 ⁴⁷	Single center, retrospective 2000 - 2015 FU: n.a.	35	54% (19)	3 – 30 (18)
Sato et al, 2017 ¹⁹	Retrospective 2000 - 2013 FU IMRT group: 1.1 – 11.7 (4.9) FU PRT group: 0.6 – 7.2 (2.6)	79	35.4% (28)	no recurrence after 5 years
Tensaouti et al, 2017 ²⁰	Multicenter, retrospective 2000 - 2013 FU: (4.5)	202	41.6% (84)	n.a.
Venkatramani et al, 2013 ⁴⁸	Prospective, multicenter 2004 - 2009 FU: (3.5)	19	47% (9)	4 – 31 (12)
Atypical teratoid rhabdoid tumor				
Bartelheim et al, 2016 ²⁴	Multicenter, prospective 2005 - 2009 FU: 5 – 8 (6.4)	31	52% (15)	1 – 37 (6.5)
Benesch et al, 2014 ²⁵	Multicenter, retrospective 2005 - 2011 FU : 0.6 – 6.9 (1.3)	19	74% (14)	(14)
Chi et al, 2009 ²⁶	Multicenter, prospective 2004 – 2006 FU: up to 2.9	20	40% (8)	1.2 – 26 (5.4)

Perreault et al, 2013 and 2014 ^{9,10}	Two centers, retrospective 2000 – 2011 FU: 0.16 – 5.4 (0.5)	10	40% (4)	2.75 – 9 (5.5)
Sung et al, 2016 ²⁷	Prospective 2004 – 2012 FU: 3.2 – 9 (5.3)	13	69% (9)	1 – 73 (5)
Zaky et al, 2014 ²⁸	Prospective, multicenter 2003 – 2009 FU: n.a.	19	73% (11)	0.8 – 39.3 (4.1)
Central nervous system primitive neuroectodermal tumors (CNS-PNET), Pineoblastoma (PBL)				
Friedrich et al, 2013 ³⁰	Multicenter, prospective 2001 - 2005 FU: 2.1 – 9.6. (8.3)	17 CNS-PNET and PBL	76% (13)	2.3 – 8.8 (5.0)
Gerber at al, 2014 ³¹	Multicenter, prospective 2001 - 2005 FU: 5.2 – 10.0 (7.0)	26 CNS-PNET and PBL	42% (11)	6 – 22.8 (15.6)
Perreault et al, 2013 and 2014 ^{9,10}	Retrospective, 2 center 2000 – 2011 FU: 0.25 – 11.4 (3.7)	25 Supratentorial PNET only	56% (14)	3 – 54 (11.5)
High-grade glioma (HGG) and Diffuse intrinsic pons glioma (DIPG)				
Macy et al, 2017 ³⁵	Prospective 2009 – 2012 FU up to 3.7	45 DIPG n=25 HGG n=20	75% (34) at 1 year	n.a.
Wolff et al, 2011 ³⁶	Prospective 2002 - 2003	30 DIPG and HGG	EFS at 1, 2 and 5 years = 43, 20 and 13%	n.a.

Abbreviations: CNS-PNET= central nervous system primitive neuroectodermal tumor; DIPG= diffuse intrinsic pons glioma; FU= follow-up; HGG= high grade glioma; IMRT= intensity-modulated radiation therapy; PBL= pineoblastoma; PRT= proton-beam radiation therapy; SHH= sonic hedgehog

TABLE 2 Summary of the most important findings from the eligible studies on secondary malignant neoplasm, intracerebral vascular malformation and white matter lesion

Study/ Year	Trial type Year of treatment FU, y, median	Number of patients	Primary tumor biology	Number of SMN and biology	Latency, y, median
Secondary malignant neoplasm (SMN)					
Dufour et al, 2014 ¹¹	Single center 2001 – 2010 FU: 0.8 – 11.3 (4.4)	24	MB	4.1% (1/24) - 1x HGG	After 9.3
Karremann et al, 2015 ³⁷	Multicenter, prospective 1995 - 2007 FU: 0 – 13.8 (1.0)	1228	HGG and DIPG	0.16% (2/1228) - 1x MGM - 1x PNET	2.4 (PNET) and 10.2 (MGM)
Massimino et al, 2011 ³⁸	Multicenter, prospective 1994 – 2003 FU: 1.2 – 15.0 (8.3)	41	EPN	2.4% (1/41) - 1x HGG	6.0
Packer et al, 2013 ³⁹	Multicenter 1996 – 2000 FU: 0.2 – 13.7 (9.7)	379	MB	1.8% (7/379) - 6x HGG - 1x LGG	3.7 – 10.3 (6.5)
Sabel et al, 2016 ⁷	Multicenter, prospective 2001 – 2006 FU: (7.8)	338	MB	0.6% (2/338) - 1x DIPG - 1x HGG	5.1 (DIPG) and 4.6 (HGG)
Von Hoff et al, 2009 ⁴⁰	Multicenter, prospective 1991 – 1997 FU: (10.0)	280	MB	2.1% (6/280) - 3x HGG - 2x MGM - 1x DIPG	n.a.
Intracerebral vascular malformations (IVM)					
Study/ Year	Trial type Year of treatment FU, y, median	Number of patients	Primary tumor biology	Number of IVM	Latency, y, median
Lew et al, 2006 ⁴¹	Single center, retrospective	59	MB	31% (18/59)	1.1 – 16.1 (6.6)

	1996 – to present FU: 1 – 25.3 (7.2)				
Leukoencephalopathy/ White matter lesions (WML)					
Study/ Year	Trial type Year of treatment FU, y, median	Number of patients	Primary tumor biology	Number of WML	Latency, y, median
Brinkman et al, 2012 ⁴⁶	Single center, prospective Year of treatment: n.a. FU: average 18yr	20	MB	80% (16/20) - Grade: n.a.	12 – 25 between treatment and evaluation
Dietrich et al, 2001 ⁴⁴	Retrospective Year of treatment: n.a. FU: 0.5 – 15 (3.8)	44	MB n=28 EPN n=2 PNET n=5 PBL n=2 Other n=7	63.6% (28/44) - Grade I: n=13 - Grade II: n=2 - Grade III/IV: cystic n=10, hemorrhagic n=3	n.a.
Kellie et al, 2005 ⁴³	Multicenter, retrospective 1990s FU: 4.0 – 10.5 (6.5)	12	MB n=9 PBL n=3	100% (12/12) - Grade I n=8 - Grade II n=4	4 cases with serial MRI: grade II changes in the first year; progressive WML and lacunes after 5 and 6 years
Rueckriegel et al, 2010 ⁴⁵	Prospective Year of treatment: n.a. FU: (3.8)	17	MB	94% (16/17) - Grade I n=11 - Grade II n=5	n.a.

Abbreviations: DIPG= diffuse intrinsic pons glioma; EPN= ependymoma; FU= follow-up; HGG= high-grade glioma; LGG= low-grade glioma;
MB= medulloblastoma; MGM= meningioma; MRI= magnetic resonance imaging; PBL= pineoblastoma; PNET= primitive neuroectodermal tumor;
WML= white matter lesion