

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

3 M Otth<sup>1</sup>, K Scheinemann<sup>2,3,4</sup>

4

5 1 Swiss Childhood Cancer Registry, Institute of Social and Preventive Medicine, University of  
6 Bern, Bern, Switzerland

7 2 Division of Hematology/ Oncology, University Children's Hospital beider Basel (UKBB) and  
8 University of Basel, Switzerland

9 3 Division of Hematology/ Oncology; McMaster Children's Hospital and McMaster University  
10 Hamilton Canada

11 4 Division of Hematology/ Oncology; Hospital for children and adolescents, Kantonsspital  
12 Aarau, Switzerland

13

14

15 Corresponding author:

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

18 Phone: +0041 31 631 56 70

19 Mail: maria.otth@ispm.unibe.ch

20

21

22

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

38 **Abstract**

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

46

47

48

49

50

51

52

53

54

55

## 56 **Introduction**

57 Tumors of the central nervous system (CNS) are the second most common tumor in childhood  
58 after leukemia. The incidence is comparable in western countries (5.47/100,000 aged 0-14 years  
59 and 5.67/100,000 aged 0-19 years in the US, 2-4/100,000 aged 0-15 years in Germany and  
60 Switzerland)<sup>1,2</sup>. Advances in imaging techniques, neurosurgery, radiotherapy, chemotherapy and  
61 supportive care have increased the survival rate significantly. Five-year relative survival for all  
62 brain tumors has increased from around 60% at the end of the 1970s to around 72.5% by 2007-  
63 2013<sup>3</sup>, though the survival rate varies between different pediatric CNS tumors. When they are  
64 cured of their primary malignancy, children need regular follow-up investigations and screenings  
65 for tumor recurrence and long-term side effects caused by chemotherapy, radiotherapy, surgery  
66 or the tumor itself. For most tumors, a national and/or international treatment protocol  
67 recommends procedures for initial diagnosis, treatment and follow up, but these  
68 recommendations usually cover only the first five or ten years after the end of treatment.

69  
70 This review summarizes the most important findings detectable on imaging ten years or more  
71 after the end of treatment for pediatric high-grade brain tumors, which includes the period of  
72 possible tumor recurrence. We also summarize possible long-term sequelae visible on imaging  
73 (secondary malignant neoplasm, vascular complications, and white matter disease) caused by the  
74 treatment.

75

## 76 **Methods**

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

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

87 Inclusion criteria for all publications are diagnosis of a high-grade brain tumor and age at first  
88 tumor diagnosis of 0-18 years. We also included publications with patient aged >18 years if the  
89 proportion of the pediatric population was described separately. An additional inclusion criterion  
90 for tumor recurrence was diagnosis after 1999; these studies have comparable and less  
91 heterogeneous treatment modalities, especially for radiotherapy. We only evaluated time to first  
92 recurrence. Secondary malignant neoplasm, intracerebral vascular malformation, and  
93 leukoencephalopathy have separate inclusion criteria for the year of first tumor diagnosis (after  
94 1989) and year of publication (after 1999).

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

99

## 100 **Results**

### 101 **Tumor recurrence**

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

104

105 Medulloblastoma (MB)

106 Medulloblastoma make up 15-30% of all brain tumors and are the second most common brain  
107 tumor after astrocytoma<sup>4</sup>. Around 50% develop before the age of 5 years. Initial metastatic  
108 disease is present in about one third<sup>5,6</sup>.

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

115

116 Ependymoma (EPN)

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

120 30 – 54% of patients relapsed between 1 month and 8.6 years from diagnosis, with am mean of  
121 12 to 19 month<sup>9,17-20</sup>. No data concerning symptomatic or asymptomatic recurrence are available.

122

123 Atypical teratoid rhabdoid tumor (ATRT)

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

130  
131 Central nervous system primitive neuroectodermal tumors (CNS-PNET), Pineoblastoma (PBL)  
132 CNS-PNET and PBL represent 2.5% - 4.8% and 0.6% of all CNS tumors respectively<sup>4,29</sup>. In the  
133 reviewed literature, initial metastatic disease was present 35% and 48% respectively<sup>10,30</sup>.  
134 The rate of recurrence was between 42% and 76%<sup>10,30,31</sup>. The latest manifestation occurred after  
135 4.5 years in a patient with CNS-PNET<sup>10</sup>. No data concerning symptomatic or asymptomatic  
136 recurrence available.

137  
138 High-grade glioma (HGG) and Diffuse intrinsic pons glioma (DIPG)  
139 HGG together with DIPG represent 8 - 17% of all CNS tumors in childhood and adolescence up  
140 to 19 years of age and are responsible for a relevant part of mortality (up to 40% of all brain  
141 tumors)<sup>4,32,33</sup>. According to data from four consecutive German HGG protocols, about 3% have  
142 initial metastatic disease<sup>34</sup>.  
143 The rate of progressive disease after one year was 75% in the study from Macy et al<sup>35</sup>. The event  
144 free-survival after one year was higher (43%) according to Wolff et al<sup>36</sup>. The 5-year event-free  
145 survival in this cohort was 13%.

146

147 **Radiological long-term sequelae**

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

150

151 Secondary malignant neoplasia

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

162

163 Intracerebral vascular malformations

164 Only one study assessing radiation-induced cavernoma in medulloblastoma patients fulfilled the  
165 inclusion criteria<sup>41</sup>. During the observation period of mean 7.2 years, 31% developed at least one  
166 intracerebral cavernoma. The cumulative incidence rate was 5.6%, 14% and 43% 3, 5 and 10  
167 years following radiotherapy for MB. Time to detection of a vascular malformation lied between  
168 1.1 and 16.1 years with a median of 6.6 years. One out of 18 patients had clinical symptoms at

169 diagnosis. He presented five years after treatment with seizure, headache, and emesis. All  
170 patients received radiotherapy to the brain.  
171  
172 Leukoencephalopathy/ White matter lesions  
173 WML is a well-known late effect after treatment for pediatric brain tumors, either after focal  
174 irradiation or after low dose craniospinal radiotherapy and chemotherapy<sup>42,43</sup>. Depending on the  
175 severity, mostly studies classify WML in grade 1-3, rarely up to grade 4. Grade 1 lesions  
176 correspond to small areas with high signal in T2\* and FLAIR in MRI. These lesions increase in  
177 grade 2 and become cystic or hemorrhagic in grade 3 and 4 lesions<sup>44</sup>. These changes can occur in  
178 parallel with an increase in subarachnoidal space and ventriculomegaly<sup>43</sup>. Different grades of  
179 WML can manifest in the same patient<sup>42-45</sup>. The incidence of WML lies between 33% and  
180 100%<sup>42-46</sup>. Two studies included MB only<sup>42,45,46</sup>; the remaining two include more than one  
181 biological type of brain tumor<sup>43,44</sup>. All patients received different combinations of chemotherapy  
182 and radiotherapy. The percentage of grade 1 lesions in each study ranges from 33 to 66%. Grade  
183 II lesions and grade III lesions were visible in 7-33% and 29% respectively.

184

## 185 **Discussion**

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

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

193  
194 Radiotherapy is a known risk factor for developing SMN in the previously irradiated field. Data  
195 from the large Childhood Cancer Survivor Study (CCSS) show that the risk for SMN in the brain  
196 increases as the diagnosis recedes. Results from large studies emphasise a linear dose-response-  
197 relationship between meningioma and glioma as SMN with a steady increase of occurrence for  
198 both tumors over time (cumulative incidence 3.3% at 25 years; 3.5% at 30 years)<sup>49,50</sup>. Most of  
199 the SMN in the reviewed literature are high-grade tumors. Only two studies reported occurrence  
200 of secondary meningioma<sup>37,40</sup>. Studies with longer follow-up periods show a larger proportion of  
201 secondary meningioma. In the CCSS cohort, the cumulative incidence of benign meningioma  
202 was 3.3% after a median follow-up of 19.6 years<sup>51</sup>. The latency period for SMN in the brain is  
203 very heterogeneous in the reviewed literature (2.4 to 10.3 years) and the development of SMN  
204 follows no predictable pattern. For slowly growing tumors (e.g. meningioma), the prognosis is  
205 not inferior if the tumor is diagnosed due to clinical symptoms compared to earlier detection by  
206 surveillance MRI. Data of women with newly diagnosed meningioma during pregnancy support  
207 this suggestion<sup>52-54</sup>. In case of absent neurological symptoms or deterioration, the management  
208 provides tight follow-up and surgery after delivery. The interval between diagnosis and surgery  
209 can thereby last up to several weeks<sup>52-54</sup>. To detect fast-growing secondary brain tumors (e.g.  
210 GBM) in an early stage, the interval between the scans would have to be very short. Even though  
211 the possibility is high to miss the tumor on MRI because the tumor was not visible on the  
212 previous but manifests clinically before the subsequent examination. In summary, it is not  
213 possible to recommend regular screening for early detection of SMN.

214  
215 Cavernoma occur more often in previously irradiated patients and detection rate depends on  
216 imaging techniques. The prevalence of cavernoma in the reviewed study is 31%. This prevalence  
217 is higher than in non-irradiated children and young adults with a prevalence of 0.6%<sup>55</sup> and also  
218 higher than in other publications including patients partially diagnosed before 1990 with rates of  
219 3.4% and 4.2%<sup>56,57</sup>. Different MRI techniques could cause some of these differences. In the  
220 study from Burn et al. no T2\*-weighted imaging was performed<sup>56</sup>. This technique is sensitive to  
221 detect blood artefacts and was used in the reviewed study. Studies including patients from past  
222 eras, not using specific MR techniques, probably underestimate the prevalence of cavernoma.  
223 Cavernoma bear the risk of spontaneous bleeding. In the study from Lew et al. 20 lesions were  
224 longitudinally followed<sup>41</sup>. They increased in size in 70% of cases, were stable in 15%, and a  
225 decreased in 15%. Despite an increase in size in 70% of cases, no patient suffered from acute  
226 bleeding during the follow-up period. The hemorrhage rate in non-irradiated children is 3.3%  
227 and 1.6% per patient-year respectively<sup>55,58</sup>. Other publications show a bleeding rate for radiation-  
228 induced cavernoma of 10%<sup>59</sup>. Radiation dose and time of follow-up may have an effect on the  
229 development of cavernoma. Unfortunately, the reviewed study did not comment on the possible  
230 effect of radiation dose. Cutsforth et al. showed, that patients treated with higher radiation doses  
231 had a shorter period to detection of cavernoma<sup>59</sup>. Burn et al. showed no correlation between  
232 radiation dose and the latency period<sup>56</sup>. According to Lew et al. with increasing time from end  
233 of treatment, the cumulative incidence of cavernoma increases<sup>41</sup>. With the knowledge of the  
234 dynamic behaviour in the natural course of cavernoma, we recommend a wait-and-see strategy  
235 with close follow-up imaging in case of an asymptomatic incidental finding. Due to the wide

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

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

249  
250 Most WML in the reviewed literature are grade 1. In the cohort from Dietrich et al., no child  
251 with WML suffered from neurological deficits, but specific neuropsychological testing was not  
252 performed. In three studies, imaging by conventional MRI was completed by the measurement of  
253 white matter anisotropy, performed by fractional anisotropy (FA) <sup>42,45,46</sup>. Results show a relevant  
254 reduction of FA in selected parts of the brain in previously irradiated children compared to non-  
255 irradiated brains. There seems to be a correlation between FA-reduction and younger age at  
256 radiotherapy as well as a time span of more than 5 years after radiation. A reduced FA or white  
257 matter integrity shows a correlation with lower cognitive outcome and executive functions<sup>42,46</sup>. It  
258 seems that special imaging modalities (e.g. diffusion weighted imaging, measurement of

259 anisotropy) are more sensitive in detection of white matter lesions than T2 weighted images  
260 alone<sup>42</sup>. The consequences of detected WML of any grade and the implications for therapeutic  
261 interventions are the focus of current research. We assume that early intervention, already  
262 preventive, with specific neuropsychological training help these patients to prevent the  
263 development or progression of impaired cognitive and executive functions.

264

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

273

274 If a patient has strong new headache or neurological symptoms 10 years or more after treatment  
275 for a high-grade brain tumor, we recommend prompt imaging, including appropriate sequences  
276 for vascular diseases. If imaging reveals a cavernoma in a critical region, we recommend regular  
277 follow-up imaging<sup>62</sup>. We do not recommend surveillance imaging for small cavernoma in non-  
278 critical regions<sup>41</sup>.

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

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

283

## 284 **Conflict of Interest Statement**

285 There is no conflict of interest

286

## 287 **Acknowledgements**

288 ---

289

290

## 291 **References**

- 292 1. Chambal L, Gudo ES, Carimo A, et al. HBV infection in untreated HIV-infected Adults in Maputo,  
293 Mozambique. *Open Forum Infectious Diseases*. 2017;4:S657.
- 294 2. SCCR. Annual\_Report\_SCCR\_2015\_2016. 2016;  
295 [https://www.kinderkrebsregister.ch/fileadmin/KKR08/uploads/pdf/Jahresberichte/Annual\\_Report\\_SCCR\\_2015\\_2016\\_Einzel\\_web.pdf](https://www.kinderkrebsregister.ch/fileadmin/KKR08/uploads/pdf/Jahresberichte/Annual_Report_SCCR_2015_2016_Einzel_web.pdf).  
296
- 297 3. Coetzee J, Hunt G, Jaffer M, et al. HIV-1 viraemia and drug resistance amongst female sex  
298 workers in Soweto, South Africa: A cross sectional study. *PLoS One*. 2017;12(12):e0188606.
- 299 4. Kaatsch P, Rickert CH, Kuhl J, Schuz J, Michaelis J. Population-based epidemiologic data on brain  
300 tumors in German children. *Cancer*. 2001;92(12):3155-3164.
- 301 5. von Bueren AO, von Hoff K, Pietsch T, et al. Treatment of young children with localized  
302 medulloblastoma by chemotherapy alone: results of the prospective, multicenter trial HIT 2000  
303 confirming the prognostic impact of histology. *Neuro-oncology*. 2011;13(6):669-679.
- 304 6. Scheinemann K BE. *Pediatric neuro-oncology*. Springer New York; 2015. 127 p.
- 305 7. Sabel M, Fleischhack G, Tippelt S, et al. Relapse patterns and outcome after relapse in standard  
306 risk medulloblastoma: a report from the HIT-SIOP-PNET4 study. *Journal of neuro-oncology*.  
307 2016;129(3):515-524.
- 308 8. Koschmann C, Bloom K, Upadhyaya S, Geyer JR, Leary SE. Survival After Relapse of  
309 Medulloblastoma. *Journal of pediatric hematology/oncology*. 2016;38(4):269-273.
- 310 9. Perreault S, Lober RM, Carret AS, et al. Surveillance imaging in children with malignant CNS  
311 tumors: low yield of spine MRI. *Journal of neuro-oncology*. 2014;116(3):617-623.
- 312 10. Perreault S, Lober RM, Carret AS, et al. Relapse patterns in pediatric embryonal central nervous  
313 system tumors. *Journal of neuro-oncology*. 2013;115(2):209-215.
- 314 11. Dufour C, Kieffer V, Varlet P, et al. Tandem high-dose chemotherapy and autologous stem cell  
315 rescue in children with newly diagnosed high-risk medulloblastoma or supratentorial primitive  
316 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.

- 363 30. Friedrich C, von Bueren AO, von Hoff K, et al. Treatment of young children with CNS-primitive  
364 neuroectodermal tumors/pineoblastomas in the prospective multicenter trial HIT 2000 using  
365 different chemotherapy regimens and radiotherapy. *Neuro-oncology*. 2013;15(2):224-234.
- 366 31. Gerber NU, von Hoff K, Resch A, et al. Treatment of children with central nervous system  
367 primitive neuroectodermal tumors/pinealoblastomas in the prospective multicentric trial HIT  
368 2000 using hyperfractionated radiation therapy followed by maintenance chemotherapy.  
369 *International journal of radiation oncology, biology, physics*. 2014;89(4):863-871.
- 370 32. Ostrom QT, Gittleman H, Xu J, et al. CBTRUS Statistical Report: Primary Brain and Other Central  
371 Nervous System Tumors Diagnosed in the United States in 2009-2013. *Neuro-oncology*.  
372 2016;18(suppl\_5):v1-v75.
- 373 33. Scheinemann K BE. *Pediatric neuro-oncology*. Springer New York; 2015. 101 p.
- 374 34. Benesch M, Wagner S, Berthold F, Wolff JE. Primary dissemination of high-grade gliomas in  
375 children: experiences from four studies of the Pediatric Oncology and Hematology Society of the  
376 German Language Group (GPOH). *Journal of neuro-oncology*. 2005;72(2):179-183.
- 377 35. Macy ME, Kieran MW, Chi SN, et al. A pediatric trial of radiation/cetuximab followed by  
378 irinotecan/cetuximab in newly diagnosed diffuse pontine gliomas and high-grade astrocytomas:  
379 A Pediatric Oncology Experimental Therapeutics Investigators' Consortium study. *Pediatric blood  
380 & cancer*. 2017;64(11).
- 381 36. Wolff JE, Kortmann RD, Wolff B, et al. High dose methotrexate for pediatric high grade glioma:  
382 results of the HIT-GBM-D pilot study. *Journal of neuro-oncology*. 2011;102(3):433-442.
- 383 37. Karremann M, Hoffmann M, Benesch M, Kwiecien R, von Bueren AO, Kramm CM. Secondary  
384 Solid Malignancies After High-Grade Glioma Treatment in Pediatric Patients. *Pediatric  
385 hematology and oncology*. 2015;32(7):467-473.
- 386 38. Massimino M, Gandola L, Barra S, et al. Infant ependymoma in a 10-year AIEOP (Associazione  
387 Italiana Ematologia Oncologia Pediatrica) experience with omitted or deferred radiotherapy.  
388 *International journal of radiation oncology, biology, physics*. 2011;80(3):807-814.
- 389 39. Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A. Survival and secondary tumors in children with  
390 medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's  
391 Oncology Group trial A9961. *Neuro-oncology*. 2013;15(1):97-103.
- 392 40. von Hoff K, Hinkes B, Gerber NU, et al. Long-term outcome and clinical prognostic factors in  
393 children with medulloblastoma treated in the prospective randomised multicentre trial HIT'91.  
394 *European journal of cancer (Oxford, England : 1990)*. 2009;45(7):1209-1217.
- 395 41. Lew SM, Morgan JN, Psaty E, Lefton DR, Allen JC, Abbott R. Cumulative incidence of radiation-  
396 induced cavernomas in long-term survivors of medulloblastoma. *Journal of neurosurgery*.  
397 2006;104(2 Suppl):103-107.
- 398 42. Khong PL, Kwong DL, Chan GC, Sham JS, Chan FL, Ooi GC. Diffusion-tensor imaging for the  
399 detection and quantification of treatment-induced white matter injury in children with  
400 medulloblastoma: a pilot study. *AJNR American journal of neuroradiology*. 2003;24(4):734-740.
- 401 43. Kellie SJ, Chaku J, Lockwood LR, O'Regan P, Waters KD, Wong CK. Late magnetic resonance  
402 imaging features of leukoencephalopathy in children with central nervous system tumours  
403 following high-dose methotrexate and neuraxis radiation therapy. *European journal of cancer  
404 (Oxford, England : 1990)*. 2005;41(11):1588-1596.
- 405 44. Dietrich U, Wanke I, Mueller T, et al. White matter disease in children treated for malignant  
406 brain tumors. *Child's nervous system : ChNS : official journal of the International Society for  
407 Pediatric Neurosurgery*. 2001;17(12):731-738.
- 408 45. Rueckriegel SM, Driever PH, Blankenburg F, Ludemann L, Henze G, Bruhn H. Differences in  
409 supratentorial damage of white matter in pediatric survivors of posterior fossa tumors with and

- 410 without adjuvant treatment as detected by magnetic resonance diffusion tensor imaging.  
411 *International journal of radiation oncology, biology, physics*. 2010;76(3):859-866.
- 412 46. Brinkman TM, Reddick WE, Luxton J, et al. Cerebral white matter integrity and executive  
413 function in adult survivors of childhood medulloblastoma. *Neuro-oncology*. 2012;14 Suppl  
414 4:iv25-36.
- 415 47. Rootman MS, Konen O, Fried I, Toledano H. Preferential sites of metastatic relapse on MRI of  
416 initially localized ependymoma in children. *Clinical imaging*. 2017;44:12-15.
- 417 48. Venkatramani R, Ji L, Lasky J, et al. Outcome of infants and young children with newly diagnosed  
418 ependymoma treated on the "Head Start" III prospective clinical trial. *Journal of neuro-oncology*.  
419 2013;113(2):285-291.
- 420 49. Armstrong GT. Long-term survivors of childhood central nervous system malignancies: the  
421 experience of the Childhood Cancer Survivor Study. *European journal of paediatric neurology :  
422 EJPN : official journal of the European Paediatric Neurology Society*. 2010;14(4):298-303.
- 423 50. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in  
424 survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Journal of the  
425 National Cancer Institute*. 2006;98(21):1528-1537.
- 426 51. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood  
427 central nervous system malignancies in the Childhood Cancer Survivor Study. *Journal of the  
428 National Cancer Institute*. 2009;101(13):946-958.
- 429 52. Laviv Y, Bayoumi A, Mahadevan A, Young B, Boone M, Kasper EM. Meningiomas in pregnancy:  
430 timing of surgery and clinical outcomes as observed in 104 cases and establishment of a best  
431 management strategy. *Acta neurochirurgica*. 2017.
- 432 53. Kanaan I, Jallu A, Kanaan H. Management Strategy for Meningioma in Pregnancy: A Clinical  
433 Study. *Skull base : official journal of North American Skull Base Society [et al]*. 2003;13(4):197-  
434 203.
- 435 54. Constantin Dumitrescu B GTL, Radu Gorgan M. Pregnant woman with an intracranial  
436 meningioma – case report and review of the literature. *Romanian Neurosurg*. 2014.
- 437 55. Al-Holou WN, O'Lynnner TM, Pandey AS, et al. Natural history and imaging prevalence of  
438 cavernous malformations in children and young adults. *Journal of neurosurgery Pediatrics*.  
439 2012;9(2):198-205.
- 440 56. Burn S, Gunny R, Phipps K, Gaze M, Hayward R. Incidence of cavernoma development in children  
441 after radiotherapy for brain tumors. *Journal of neurosurgery*. 2007;106(5 Suppl):379-383.
- 442 57. Gastelum E, Sear K, Hills N, et al. Rates and characteristics of radiographically detected  
443 intracerebral cavernous malformations after cranial radiation therapy in pediatric cancer  
444 patients. *Journal of child neurology*. 2015;30(7):842-849.
- 445 58. Gross BA, Du R, Orbach DB, Scott RM, Smith ER. The natural history of cerebral cavernous  
446 malformations in children. *Journal of neurosurgery Pediatrics*. 2015:1-6.
- 447 59. Cutsforth-Gregory JK, Lanzino G, Link MJ, Brown RD, Jr., Flemming KD. Characterization of  
448 radiation-induced cavernous malformations and comparison with a nonradiation cavernous  
449 malformation cohort. *Journal of neurosurgery*. 2015;122(5):1214-1222.
- 450 60. Ullrich NJ, Robertson R, Kinnamon DD, et al. Moyamoya following cranial irradiation for primary  
451 brain tumors in children. *Neurology*. 2007;68(12):932-938.
- 452 61. Wu YH, Chang FC, Liang ML, et al. Incidence and long-term outcome of postradiotherapy  
453 moyamoya syndrome in pediatric patients with primary brain tumors: a single institute  
454 experience in Taiwan. *Cancer medicine*. 2016;5(8):2155-2160.
- 455 62. Lee JW, Kim DS, Shim KW, et al. Management of intracranial cavernous malformation in  
456 pediatric patients. *Child's nervous system : ChNS : official journal of the International Society for  
457 Pediatric Neurosurgery*. 2008;24(3):321-327.

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

<b>Study/ Year</b>	<b>Trial type Year of diagnosis FU, y, median</b>	<b>Number of patients</b>	<b>Number of relapse % (n)</b>	<b>Latency from primary diagnosis to relapse, mo, median</b>
<b>Medulloblastoma</b>				
Dufour et al, 2014 <sup>11</sup>	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 <sup>8</sup>	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 <sup>12</sup>	Single center, retrospective 2003 - 2011 FU: 1.9 – 9.1 (6.5)	16	18.7% (3)	n.a.
Perreault et al, 2013 and 2014 <sup>9,10</sup>	Two centers, retrospective 2000 – 2011 FU: 0.23 – 11.8 (4.3)	89	29.2% (26)	0.5 – 76 (16)
Sabel et al, 2016 <sup>7</sup>	Multicenter, prospective 2001 - 2006 FU: (7.8)	338	21% (72)	2 - 95 (26)
Sung et al, 2013 <sup>13</sup>	Single center, prospective 2005 - 2010 FU: 1.9 – 6.8 (3.8)	20	20% (4)	6 – 21
Von Bueren at al, 2011 <sup>5</sup>	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 <sup>14</sup>	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)

<b>Ependymoma</b>				
Massimio et al, 2016 <sup>18</sup>	Multicenter, prospective 2002 - 2014 FU: 3.4 – 9.1 (5.6)	160	30.6% (49)	4 – 103 (19)
Perreault et al, 2014 <sup>9</sup>	Two centers, retrospective 2000 – 2011 FU: 0.5 – 11.1 (3.9)	52	50% (26)	1 – 65 (16)
Rootman et al, 2017 <sup>47</sup>	Single center, retrospective 2000 - 2015 FU: n.a.	35	54% (19)	3 – 30 (18)
Sato et al, 2017 <sup>19</sup>	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 <sup>20</sup>	Multicenter, retrospective 2000 - 2013 FU: (4.5)	202	41.6% (84)	n.a.
Venkatramani et al, 2013 <sup>48</sup>	Prospective, multicenter 2004 - 2009 FU: (3.5)	19	47% (9)	4 – 31 (12)
<b>Atypical teratoid rhabdoid tumor</b>				
Bartelheim et al, 2016 <sup>24</sup>	Multicenter, prospective 2005 - 2009 FU: 5 – 8 (6.4)	31	52% (15)	1 – 37 (6.5)
Benesch et al, 2014 <sup>25</sup>	Multicenter, retrospective 2005 - 2011 FU : 0.6 – 6.9 (1.3)	19	74% (14)	(14)
Chi et al, 2009 <sup>26</sup>	Multicenter, prospective 2004 – 2006 FU: up to 2.9	20	40% (8)	1.2 – 26 (5.4)

Perreault et al, 2013 and 2014 <sup>9,10</sup>	Two centers, retrospective 2000 – 2011 FU: 0.16 – 5.4 (0.5)	10	40% (4)	2.75 – 9 (5.5)
Sung et al, 2016 <sup>27</sup>	Prospective 2004 – 2012 FU: 3.2 – 9 (5.3)	13	69% (9)	1 – 73 (5)
Zaky et al, 2014 <sup>28</sup>	Prospective, multicenter 2003 – 2009 FU: n.a.	19	73% (11)	0.8 – 39.3 (4.1)
<b>Central nervous system primitive neuroectodermal tumors (CNS-PNET), Pineoblastoma (PBL)</b>				
Friedrich et al, 2013 <sup>30</sup>	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 <sup>31</sup>	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 <sup>9,10</sup>	Retrospective, 2 center 2000 – 2011 FU: 0.25 – 11.4 (3.7)	25 Supratentorial PNET only	56% (14)	3 – 54 (11.5)
<b>High-grade glioma (HGG) and Diffuse intrinsic pons glioma (DIPG)</b>				
Macy et al, 2017 <sup>35</sup>	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 <sup>36</sup>	Prospective 2002 - 2003	30 DIPG and HGG	EFS at 1, 2 and 5 years = 43, 20 and 13%	n.a.

Published in final edited form as: *Pediatr Blood Cancer*. 2018 Nov;65(11):e27311.  
doi: 10.1002/pbc.27311.

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
<b>Secondary malignant neoplasm (SMN)</b>					
Dufour et al, 2014 <sup>11</sup>	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 <sup>37</sup>	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 <sup>38</sup>	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 <sup>39</sup>	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 <sup>7</sup>	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 <sup>40</sup>	Multicenter, prospective 1991 – 1997 FU: (10.0)	280	MB	2.1% (6/280) - 3x HGG - 2x MGM - 1x DIPG	n.a.
<b>Intracerebral vascular malformations (IVM)</b>					
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 <sup>41</sup>	Single center, retrospective	59	MB	31% (18/59)	1.1 – 16.1 (6.6)

	1996 – to present FU: 1 – 25.3 (7.2)				
<b>Leukoencephalopathy/ White matter lesions (WML)</b>					
<b>Study/ Year</b>	<b>Trial type Year of treatment FU, y, median</b>	<b>Number of patients</b>	<b>Primary tumor biology</b>	<b>Number of WML</b>	<b>Latency, y, median</b>
Brinkman et al, 2012 <sup>46</sup>	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 <sup>44</sup>	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 <sup>43</sup>	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 <sup>45</sup>	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