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	
	1

- 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	

# 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

## 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

Tumors of the central nervous system (CNS) are the second most common tumor in childhood 57 after leukemia. The incidence is comparable in western countries (5.47/100,000 aged 0-14 years 58 and 5.67/100,000 aged 0-19 years in the US, 2-4/100,000 aged 0-15 years in Germany and 59 Switzerland)<sup>1,2</sup>. Advances in imaging techniques, neurosurgery, radiotherapy, chemotherapy and 60 supportive care have increased the survival rate significantly. Five-year relative survival for all 61 brain tumors has increased from around 60% at the end of the 1970s to around 72.5% by 2007-62 2013<sup>3</sup>, though the survival rate varies between different pediatric CNS tumors. When they are 63 64 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 65 or the tumor itself. For most tumors, a national and/or international treatment protocol 66 recommends procedures for initial diagnosis, treatment and follow up, but these 67 recommendations usually cover only the first five or ten years after the end of treatment. 68 69 This review summarizes the most important findings detectable on imaging ten years or more 70 after the end of treatment for pediatric high-grade brain tumors, which includes the period of 71 possible tumor recurrence. We also summarize possible long-term sequelae visible on imaging 72 (secondary malignant neoplasm, vascular complications, and white matter disease) caused by the 73 treatment. 74

75

#### 76 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

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

- Table 1 provides an overview of the most important findings from the eligible studies on tumorrecurrence.
- 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  $^{5,6}$ .
- 109 Tumor recurrence rate was between 18.7%-40%. <sup>5,7-14</sup>. No relapse occurred more than ten years
- after diagnosis. The longest documented latency period was 7.9 years, in a patient with standard
- risk MB<sup>7</sup>. The proportion of late relapse, arbitrarily defined as >5 years from diagnosis, is
- mentioned in two publications and is 8% and 7% respectively<sup>7,8</sup>. According to Sabel et al. and
- Perreault et al. 69% and 46% of all recurrences were asymptomatic and detected by surveillance
  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>.
- 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.
- About two-third of newly diagnosed ATRT occur before the age of 3 years. In 21-30%,
- 126 dissemination is present at initial diagnosis $^{21-23}$ .
- 127 Relapse occur in 40 74% of patients with a mean latency period around 5 month and the latest
- 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
- reviewed literature, initial metastatic disease was present 35% and 48% respectively  $^{10,30}$ .

134 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-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

to 19 years of age and are responsible for a relevant part of mortality (up to 40% of all brain

- tumors)<sup>4,32,33</sup>. According to data from four consecutive German HGG protocols, about 3% have
  initial metastatic disease<sup>34</sup>.
- 143 The rate of progressive disease after one year was 75% in the study from Macy et  $al^{35}$ . The event
- 144 free-survival after one year was higher (43%) according to Wolff et al<sup>36</sup>. The 5-year event-free

survival in this cohort was 13%.

### 147 Radiological long-term sequelae

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

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

with a maximum of 15.0 years  $^{7,11,37-40}$ . The primary diagnosis was either medulloblastoma,

154 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

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

available from five studies, ranging from 2.4 years (PNET) to 10.3 years (high-grade

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

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

inclusion criteria<sup>41</sup>. 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

- 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

- diagnosis. He presented five years after treatment with seizure, headache, and emesis. Allpatients 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
- irradiation or after low dose craniospinal radiotherapy and chemotherapy<sup>42,43</sup>. Depending on the
- 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
- grade 2 and become cystic or hemorrhagic in grade 3 and 4 lesions<sup>44</sup>. These changes can occur in
- 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  $100\%^{42-46}$ . Two studies included MB only<sup>42,45,46</sup>; the remaining two include more than one
- biological type of brain tumor<sup>43,44</sup>. All patients received different combinations of chemotherapy
- 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

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<sup>5,7-14,18-20,24-28,30,31,35,36,47,48</sup>. 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 oftreatment.

193

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

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 $0.6\%^{55}$ 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 $10\%^{59}$ . 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

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

A second cerebral vascular disorder observed after radiotherapy to the brain is moyamoya. Most 238 239 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 240 for moyamoya independent of radiotherapy and separate guidelines for surveillance imaging 241 exist. After excluding these patients from otherwise eligible studies, the number of patients 242 without moyamoya is far less than  $10^{60,61}$ . Both studies showed that radiation to the circle of 243 Willisi or the supratentorial region is a risk factor for moyamoya. In the study from Ullrich et al., 244 the high rate of optic pathway glioma and therefore patients with probably having NF1 might 245 bias this observation. In the population of Wu et al., only 25% suffered from optic pathway 246 glioma, but all received suprasellar radiotherapy. Therefore, suprasellar radiotherapy seems to be 247 a risk factor for moyamoya. 248

249

Most WML in the reviewed literature are grade 1. In the cohort from Dietrich et al., no child 250 with WML suffered from neurological deficits, but specific neuropsychological testing was not 251 performed. In three studies, imaging by conventional MRI was completed by the measurement of 252 white matter anisotropy, performed by fractional anisotropy (FA)<sup>42,45,46</sup>. Results show a relevant 253 reduction of FA in selected parts of the brain in previously irradiated children compared to non-254 255 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 matter integrity shows a correlation with lower cognitive outcome and executive functions<sup>42,46</sup>. It 257 258 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 alone<sup>42</sup>. The consequences of detected WML of any grade and the implications for therapeutic 260 interventions are the focus of current research. We assume that early intervention, already 261 preventive, with specific neuropsychological training help these patients to prevent the 262 development or progression of impaired cognitive and executive functions. 263 264 The small number of studies that were eligible after we applied strict inclusion criteria, 265 especially the limits imposed by year of diagnosis and the requirement for at least 10 patients 266 limited our review. Since diagnoses were 1990 and onwards, the follow-up period was short, 267 which probably biases the distribution towards more high-grade SMN and underestimates the 268 rate of low-grade SMN. The large differences in cumulative incidence rate of vascular 269 270 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 271 follow-up care. 272 273 If a patient has strong new headache or neurological symptoms 10 years or more after treatment 274 for a high-grade brain tumor, we recommend prompt imaging, including appropriate sequences 275 for vascular diseases. If imaging reveals a cavernoma in a critical region, we recommend regular 276 follow-up imaging <sup>62</sup>. We do not recommend surveillance imaging for small cavernoma in non-277 critical regions<sup>41</sup>. 278

We found that screening imaging more than 10 years after completing treatment for childhoodhigh-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.

283

### 284 **Conflict of Interest Statement**

- 285 There is no conflict of interest
- 286
- 287 Acknowledgements
- 288 ---
- 289
- 290

### 291 **References**

- 2921.Chambal L, Gudo ES, Carimo A, et al. HBV infection in untreated HIV-infected Adults in Maputo,293Mozambique. Open Forum Infectious Diseases. 2017;4:S657.
- 294 2. SCCR. Annual\_Report\_SCCR\_2015\_2016. 2016;
- 295https://www.kinderkrebsregister.ch/fileadmin/KKR08/uploads/pdf/Jahresberichte/Annual\_Rep296ort\_SCCR\_2015\_2016\_Einzel\_web.pdf.
- 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.
- 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.
- 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.
- 304 6. Scheinemann K BE. *Pediatric neuro-oncology*. Springer New York; 2015. 127 p.
- 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.
- 3088.Koschmann C, Bloom K, Upadhyaya S, Geyer JR, Leary SE. Survival After Relapse of309Medulloblastoma. Journal of pediatric hematology/oncology. 2016;38(4):269-273.
- 3109.Perreault S, Lober RM, Carret AS, et al. Surveillance imaging in children with malignant CNS311tumors: low yield of spine MRI. Journal of neuro-oncology. 2014;116(3):617-623.
- 31210.Perreault S, Lober RM, Carret AS, et al. Relapse patterns in pediatric embryonal central nervous313system tumors. Journal of neuro-oncology. 2013;115(2):209-215.
- 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 patients with intracranial ependymoma. Radiotherapy and oncology : journal of the European 338 339 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. 29. 362 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 Solid Malignancies After High-Grade Glioma Treatment in Pediatric Patients. Pediatric 384 385 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. 45. 408 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

410 411 412	46	without adjuvant treatment as detected by magnetic resonance diffusion tensor imaging. International journal of radiation oncology, biology, physics. 2010;76(3):859-866. Brinkman TM, Beddick WF, Luxton L, et al. Cerebral white matter integrity and executive
413 414	10.	function in adult survivors of childhood medulloblastoma. <i>Neuro-oncology</i> . 2012;14 Suppl 4:iv25-36.
415 416	47.	Rootman MS, Konen O, Fried I, Toledano H. Preferential sites of metastatic relapse on MRI of initially localized ependymoma in children. <i>Clinical imaging.</i> 2017;44:12-15.
417 418 410	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. <i>Journal of neuro-oncology</i> . 2012;112(2):285–201
420 421	49.	Armstrong GT. Long-term survivors of childhood central nervous system malignancies: the experience of the Childhood Cancer Survivor Study. <i>European journal of paediatric neurology :</i>
422 423	50.	<i>EJPN : official journal of the European Paediatric Neurology Society.</i> 2010;14(4):298-303. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in
424 425 426	Г1	Survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. <i>Journal of the</i> National Cancer Institute. 2006;98(21):1528-1537.
426 427 428	51.	central nervous system malignancies in the Childhood Cancer Survivor Study. <i>Journal of the</i> National Cancer Institute, 2009:101(13):946-958
429 430	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
431 432	53	management strategy. Acta neurochirurgica. 2017. Kanaan L. Jallu A. Kanaan H. Management Strategy for Meningioma in Pregnancy: A Clinical
433 434	50.	Study. Skull base : official journal of North American Skull Base Society [et al]. 2003;13(4):197- 203.
435 436	54.	Constantin Dumitrescu B GTL, Radu Gorgan M. Pregnant woman with an intracranial meningioma – case report and review of the literature. <i>Romanian Neurosurg.</i> 2014.
437 438 439	55.	Al-Holou WN, O'Lynnger TM, Pandey AS, et al. Natural history and imaging prevalence of cavernous malformations in children and young adults. <i>Journal of neurosurgery Pediatrics</i> . 2012;9(2):198-205.
440 441	56.	Burn S, Gunny R, Phipps K, Gaze M, Hayward R. Incidence of cavernoma development in children after radiotherapy for brain tumors. <i>Journal of neurosurgery</i> . 2007;106(5 Suppl):379-383.
442 443 444	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. <i>Journal of child neurology</i> , 2015:30(7):842-849.
445 446	58.	Gross BA, Du R, Orbach DB, Scott RM, Smith ER. The natural history of cerebral cavernous malformations in children. <i>Journal of neurosurgery Pediatrics</i> . 2015:1-6.
447 448 449	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. <i>Journal of neurosurgery</i> . 2015;122(5):1214-1222.
450 451	60.	Ullrich NJ, Robertson R, Kinnamon DD, et al. Moyamoya following cranial irradiation for primary brain tumors in children. <i>Neurology</i> . 2007;68(12):932-938.
452 453 454	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. <i>Cancer medicine</i> . 2016;5(8):2155-2160.
455 456 457	62.	Lee JW, Kim DS, Shim KW, et al. Management of intracranial cavernous malformation in pediatric patients. <i>Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery</i> . 2008;24(3):321-327.

Study/ Year	Trial type	Number of	Number of	Latency from primary
	Year of diagnosis	patients	relapse % (n)	diagnosis to relapse, mo,
	FU, y, median			median
Medulloblastoma				
Dufour et al, 2014 <sup>11</sup>	Single center, prospective 2001 - 2010	21	28.5% (6)	9.2 – 74.4 (19.5)
W 1 00168	FU: 0.8 – 11.3 (4.4)	47		
Koschmann et al, 2016°	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)

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

Ependymoma				
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)
Atypical teratoid rhabdoid to	umor			
Bartelheim at 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 $2014^{9,10}$	Two centers, retrospective 2000 – 2011 FU: 0.16 – 5.4 (0.5)	10	40% (4)	2.75 – 9 (5.5)
Sung et al, 2016 <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)
Central nervous system prim	itive neuroectodermal tumors (CN	S-PNET), Pineo	oblastoma (PBL)	
Friedrich et al, 2013 <sup>30</sup>	Multicenter, prospective	17	76% (13)	2.3 - 8.8 (5.0)
	2001 - 2005	CNS-PNET		
	FU: 2.1 – 9.6. (8.3)	and PBL		
Gerber at al, $2014^{31}$	Multicenter, prospective	26	42% (11)	6 – 22.8 (15.6)
	2001 - 2005	CNS-PNET		
	FU: 5.2 – 10.0 (7.0)	and PBL		
Perreault et al, 2013 and	Retrospective, 2 center	25	56% (14)	3 – 54 (11.5)
2014 <sup>9,10</sup>	2000 - 2011	Supratentorial		
	FU: 0.25 – 11.4 (3.7)	PNET only		
High-grade glioma (HGG) an	d Diffuse intrinsic pons glioma (Dl	(PG)		
Macy et al, 2017 <sup>35</sup>	Prospective	45	75% (34) at 1 year	n.a.
	2009 - 2012	DIPG n=25		
	FU up to 3.7	HGG n=20		
Wolff et al, 2011 <sup>36</sup>	Prospective	30	EFS at 1, 2 and 5	n.a.
	2002 - 2003	DIPG and	years	
		HGG	= 43, 20 and 13%	

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