Clinical Oncology 33 (2021) e295–e304

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Feasibility of Proton Beam Therapy for Infants with Brain Tumours: Experiences from the Prospective KiProReg Registry Study

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Abstract

Aims: Proton beam therapy (PBT) has increasingly been applied for the treatment of young children when radiotherapy is needed. The treatment requires intensive multimodality care and is logistically demanding. In this analysis, we evaluated our experiences in treating infants with tumours of the central nervous system with PBT.
Materials and methods: Children younger than 2 years of age treated with PBT for central nervous system tumours enrolled in the prospective registry study KiProReg were retrospectively analysed. Information on patient characteristics, treatment, toxicities and outcome were evaluated. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE V4.0) before, during and after PBT.
Results: Between September 2013 and June 2018, 51 infants were eligible. The median age was 19 months (range 11–23 months) at the time of PBT. Tumour entities were ependymoma (51.0%), atypical teratoid rhabdoid tumour (39.0%), high-grade glioma (6.0%), pineoblastoma (2.0%) and medulloblastoma (2.0%). The prescribed median total dose was 54.0 Gy (range 45.0–59.4 Gy). Most received local radiotherapy. In four patients, craniospinal irradiation followed by a boost to the local tumour bed was applied. The median follow-up time was 42.0 months (range 7.3–86.2 months). The estimated 3-year local control, progression-free survival and overall survival rates for all patients were 62.7, 47.1 and 76.5%, respectively. During radiotherapy, 24 events of higher-grade (CTCAE $\geq$ °III) toxicities were reported. Interruption of radiotherapy for more than 2 days was due to infection ($n = 3$) or shunt complication ($n = 2$). Unexpected hospitalisation during radiotherapy affected 12 patients. Late adverse events attributable to radiotherapy included endocrinopathy (CTCAE °II; 7.8%), new onset of hearing loss (CTCAE °III; 5.8%) and visual impairment (CTCAE °IV; 1.9%). Transient radiation-induced imaging changes occurred in five patients (9.8%).
Conclusions: Our study indicates that PBT is feasible for very young children with central nervous system tumours, at least in the short term. However, it requires challenging interdisciplinary medical care and high logistical effort. For evaluation of late effects, longer follow-up and evaluation of neurocognitive outcome are desirable. More data have to be gathered to further define the role of radiotherapy in infants over time.

Key words: Brain tumours; infants; proton beam therapy; radiotherapy; very young children

Introduction

Primary intracranial malignant tumours constitute the second most common cancer type during childhood, accounting for more than 20% of all paediatric malignancies

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https://doi.org/10.1016/j.clon.2021.03.006
0936-6555/

[1]. Below the age of 2 years, astrocytoma is the most common entity, followed by ependymoma, medulloblastoma and atypical teratoid rhabdoid tumour (ATRT) [2].

Treatment of infants represents a therapeutic challenge, as this cohort is particularly vulnerable, thus requiring intensive multimodality treatment. Although radiotherapy is an effective component of the multidisciplinary treatment strategy, the role of upfront radiotherapy for very young children remains controversial [3]. Given the vulnerability of the immature and developing brain tissue, radiotherapy causes significant late adverse effects, including neurocognitive deficits, endocrine impairment, growth disturbances or hearing loss [4–6]. Therefore, many protocols attempted to postpone or avoid radiotherapy for infants and to replace radiotherapy with intensive chemotherapy (CTx) regimens as a potentially more tolerable alternative. However, although this seemed feasible for gliomas [7] and medulloblastomas [8], unsatisfactory results have been obtained for ependymoma and ATRT so far, promoting discussions on the need for early irradiation in these entities [9–12].

Due to its physical properties, proton beam therapy (PBT) allows highly conformal radiation therapy to the target volume while sparing relevant organs at risk [13]. Several planning studies have indicated a potential advantage of PBT for children with brain tumours [14–16]. Moreover, several reports have shown that these dosimetric advantages may translate into clinical benefits. Comparative studies reported a better endocrine outcome, better quality of life and no substantial impairment of intelligence quotient levels after PBT compared with conventional photon therapy [17–19]. Therefore, PBT is of increasing interest, particularly for infants. Still, radiotherapy in infants poses typical challenges regardless of optimal treatment techniques. To date, little information is available on radiation-induced toxicity for children younger than 2 years. This study reports our experiences in the treatment of infants with brain tumours with PBT, addressing typical scenarios and demands during the course of radiotherapy.

Materials and Methods

Patients

Infants were defined as children younger than 2 years of age according to the World Health Organization and the US Food and Drug Administration classification [20]. We analysed all infants treated with PBT for primary brain malignancies at our institution between September 2013 and June 2018. Patients who underwent re-irradiation were excluded from analyses. Patients were enrolled to the prospective in-house registry (KiProReg; DRKS00005363) collecting data on patient characteristics, treatment, adverse events and outcome.

Treatment

Overall strategies were applied within or according to the respective national or international protocols (Table 1). In the case of local field irradiation, patients were typically immobilised in the supine position. For craniospinal irradiation (CSI) followed by a boost to the tumour bed, children were treated in the prone position. For all patients, a thermoplastic mask and vacuum moulds were used. Treatment planning computed tomography was obtained using 1–2 mm slice thickness for all cases. Planning computed tomography was merged with planning magnetic resonance imaging (MRI) and the initial and most recent previous diagnostic MRIs. Target volume delineation and dose prescription were defined according to the respective interdisciplinary protocol. For local field or boost radiotherapy, the initial tumour volume, the postoperative tumour bed and a clinical target volume were delineated as specified within the respective protocol. A three millimetre margin was added for the planning target volume. In the case of CSI, the complete subarachnoid space was defined as the clinical target volume and extended by a 3–5 mm margin to create the planning

Table 1
Applied treatment protocols

Protocol	Diagnosis	*n*	%
EU-RHAB	Atypical teratoid rhabdoid tumour	19	37.3
DFCI0294	Atypical teratoid rhabdoid tumour	1	2.0
HIT-MED	Ependymoma Medulloblastoma Pineoblastoma	17	33.3
SIOP Ependymoma II	Ependymoma	5	9.8
HIT 2000 Interim Registry	Ependymoma	2	3.9
COG ACNS 0122	Ependymoma	2	3.9
CCG9942	Ependymoma	1	2.0
UKCCG	Ependymoma	1	2.0
HIT HGG	High-grade glioma	3	5.8
Total		51	100

CCG9942, Children's Cancer Group protocol 9942; COG, Children's Oncology Group; DFCI0294, Dana-Farber Cancer Institute trial 0294; EU-RHAB, European Rhabdoid Registry; HGG, high-grade glioma; HIT-MED, therapy guidance for patients with newly diagnosed medulloblastoma, ependymoma, central nervous system embryonal tumour and pineoblastoma; SIOP, International Society of Paediatric Oncology; UKCCG, United Kingdom Cancer Cytogenetics Group.

target volume. For all dose concepts, a generic relative biological effectiveness (RBE) factor of 1.1 (relative to that of Co-60) was assumed. Proton doses were expressed in terms of Gy (RBE) [Gy (RBE) = proton Gy × 1.1]. PBT was applied with either uniform or pencil beam scanning (PBS) for local or boost radiotherapy and with PBS for the CSI. During PBT, oncological support and application of CTx was provided by the clinic for paediatric oncology; daily deep sedation maintaining spontaneous breathing was performed by paediatric anesthesiologists, typically in an outpatient setting.

Evaluation of Adverse Events and Complications

Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0) grading system [21]. The evaluation of clinical condition, vital signs and maximal adverse events was carried out before the start of PBT (baseline), weekly during PBT, at the end of PBT and during follow-up visits. In terms of haematological toxicity, according to the applied CTCAE criteria, higher grade toxicity were defined as haemoglobin $\leq$7.9 g/100 ml, leukocytes $\leq 1.9 \times 10^9$/l, granulocytes $\leq 0.9 \times 10^9$/l, platelets $\leq 49.9 \times 10^9$/l or lymphocytes $\leq 0.9 \times 10^9$/l. Additionally, unplanned hospitalisations of at least one night, as well as any non-technical interruption of PBT were recorded during the radiotherapy course. All used medical devices and interventions were documented in the digital chart. After the end of PBT, patients were followed up at 3 months and then annually. If patients were unable to personally attend their follow-up appointments, information was collected via telephone calls, standardised questionnaires and the referring centres were contacted. Any radiotherapy-related side-effect during radiotherapy and up to 3 months thereafter was considered to be an acute adverse event. Any event presenting later than 3 months after the completion of PBT was considered to be a late adverse event. Performance status was assessed using Lansky scores [22]. Systematic neurocognitive evaluations were not included in the regular schedule of the registry.

Statistics

Follow-up time was calculated from the time of first diagnosis to the last contact or event. Descriptive statistics was performed in order to summarise the features of the cohort. Local control was defined as an absence of tumour recurrence or progression in the irradiated area. The local control rate was calculated from the initial diagnoses until the event. Progression-free survival (PFS) was defined as the time from initial diagnosis until first evidence of tumour progression (local, leptomeningeal). Overall survival was defined as the time from the initial diagnosis until death. The Kaplan–Meier method was used to estimate the local control, PFS and overall survival rates. If the respective event was not observed, the date of last contact was used for censoring. Subgroup analyses for ependymoma and ATRT were conducted. All statistical analysis was carried out using the IBM SPSS Statistics program V22.

Results

Patient and Tumour Characteristics

In total, 51 infants with a median age of 19 months (range 11–23 months) were evaluable. The cohort comprised 26 patients with ependymoma, 20 with ATRT, three with high-grade glioma, one with pineoblastoma and one with medulloblastoma. Patient characteristics are displayed in Table 2. Except for two children, all patients underwent surgery before irradiation. At least one second surgery before radiotherapy was carried out in 35.3% of the total cohort; 9.8% underwent a total of three operations before starting radiotherapy. Gross total resection was achieved in 39.2%. In 27 patients, a ventriculoperitoneal shunt was in place before radiotherapy. Most patients (78.4%) received multidrug CTx before irradiation. Following previous intrathecal CTx via Omaya/Rickham, the intraventricular reservoir

Table 2
Patient characteristics

Characteristics	*n*	%
Gender		
Female	29	56.9
Male	22	43.1
Primary tumour site		
Supratentorial	10	19.6
Infratentorial	38	74.5
Supra- and infratentorial	3	5.9
Stage		
M0	45	88.2
M1	4	7.8
M2	1	2.0
M3	1	2.0
Histology		
Ependymoma	26	51.0
WHO I	0	0
WHO II	4	15
WHO III	22	83.3
ATRT	20	39.0
HGG	3	6.0
Medulloblastoma	1	2.0
Pineoblastoma	1	2.0
Time of radiotherapy		
At initial diagnosis	47	92.2
At relapse	4	7.8
Pre-treatment		
Radiation therapy	–	–
Chemotherapy	40	78.4
Surgery	49	96.1
Gross total	20	
Subtotal	29	
Biopsy only	2	3.9

ATRT, atypical teratoid rhabdoid tumour; HGG, high-grade glioma; M0, no evidence of metastasis; M1, tumour cells identified by cerebrospinal fluid cytology; M2, intracranial metastatic tumour; M3, spinal metastatic tumour; WHO, World Health Organization.

remained during radiotherapy in 14 patients. Concomitant CTx was delivered to 25.5% of the presented cohort. Radiotherapy was used for primary treatment in 47 patients, whereas four children were treated for relapsed disease. The median time from diagnosis to the start of radiotherapy was 5 months (range 1–23 months).

Treatment Data

Radiotherapy was applied as local field radiotherapy to 47 patients, whereas CSI followed by a boost was carried out in four patients. The prescribed median total PBT dose was 54.0 Gy (RBE) [range 45.0–59.4 Gy (RBE)] applied in 30 fractions (median) with a median single dose of 1.8 Gy (RBE) (5 days per week). In the case of CSI, the dose to the CSI volume was 24 Gy (RBE), the median number of fractions was 15 and the single dose was 1.6 Gy (RBE). Patients were treated using uniform scanning (45.1%), PBS (51.0%) or combining both (3.9%). Treatment characteristics are listed in Table 3. All children required intravenous sedation to ensure reliable positioning within daily treatment. Therefore, a central venous catheter was mandatory for all children in order to avoid traumatic pain of repeated venous access or the risk of extravasation during the treatment course of several weeks. In more than half the patients (60.8%), a port catheter was used, whereas central lines (Boviac/Hickman) (35.3%) were less common.

Table 3
Treatment characteristics

Characteristics		
PBT data	Median	Range
Total dose		
Fraction no.	30	25–33
Fraction dose in Gy (RBE)	1.8	1.6–1.8
	n	%
Target volume		
Local	47	92.2
CSI + local	4	7.8
Treatment technique		
Pencil beam scanning	26	51.0
Uniform scanning	23	45.1
Both	2	3.9
Concomitant chemotherapy		
Yes	13	25.5
No	38	74.5
PBT under sedation		
Yes	51	100.0
No	0	0
Shunt		
Yes	27	52.9
No	24	47.1
Central line		
Port	31	60.8
Broviak	14	27.5
Hickman	4	7.8
Unknown	2	3.9
Enteral nutrition		
None	30	58.8
PEG/PEJ	18	35.3
Nasogastral	3	5.9
Intraventricular catheter		
None	37	72.5
Yes	14	27.5

CSI, craniospinal irradiation; PBT, proton beam therapy; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; RBE, relative biological effectiveness.

Patients with ATRT were treated according to the European Rhabdoid Registry recommendations (Version 5, 2016). Here, radiotherapy is recommended starting from ≥18 months. However, within our cohort, radiotherapy was carried out before in the case of three patients (age 11–15 months) according to the interdisciplinary study group decision because the patients were considered to be at high failure risk due to inoperable residual disease following systemic CTx.

Patients with ependymoma were treated either according to HIT-MED Guidance (2017, Version 4, DRKS00007760) recommending a lower age limit for radiotherapy of 18 months, according to the SIOP Ependymoma II trial (EudraCT: 2014-001470-34) with a lower age limit for radiotherapy of 12 months or according to the Children Oncology Group trial ACNS0121 (NCT01407744) with a lower age limit for radiotherapy of 12 months. Despite these age limits, four patients had been irradiated earlier on German study board decision due to progression during CTx. According to the international HIT High-Grade Glioma 2013 protocol (EudraCT: 2013-004187-56), children were eligible for radiotherapy at the age of 3 years. However, three younger patients were included in our cohort after study board discussion due to histology (K27 H3.1; $n = 1$), no response to CTx ($n = 1$) or because parents declined CTx ($n = 1$), respectively.

One child with a medulloblastoma was irradiated after incomplete remission following surgery, intensified induction CTx and high-dose CTx as indicated by HIT-MED Guidance. Additionally, one child with pineoblastoma was irradiated following the international HIT-MED Guidance.

In our cohort, six patients presented with metastatic disease at initial diagnosis. Of them, four children (three with ATRT and one with medulloblastoma) were treated with CSI. In two patients with disseminated disease, CSI was not applied (in one patient with ATRT due to parents' refusal and in one patient with ependymoma having remission of M1 status after CTx.

Baseline Condition

Twenty-one patients presented with one or more neurological deficits before starting PBT, including cranial nerve palsy ($n = 16$), hemiparesis ($n = 6$), bulbar palsy ($n = 5$) and fossa posterior syndrome ($n = 2$). Due to neurological impairment, nutrition support had to be provided to 21 patients before starting PBT. Devices for nutrition support were either percutaneous endoscopic gastrostomy/jejunostomy (PEG/PEJ; 86.3%) or nasogastric tubes (13.7%), respectively. Although the median Lansky score was 100% (range 60–100%), five (9.8%) patients had a Lansky score of 70% or less at baseline.

Acute Adverse Events

With regards to haematological toxicity, higher-grade events (>°II CTCAE) were reported in 16 cases, including lymphopenia ($n = 11$), thrombocytopenia ($n = 5$), anaemia ($n = 4$) and neutropenia ($n = 4$). In total, 88.8% of the patients who experienced higher-grade haematological toxicity received CTx before or during radiotherapy. Only one child receiving local radiotherapy experienced haematological toxicity without CTx before or concomitant to radiotherapy caused by iron deficiency during irradiation. Management consisted of granulocyte-colony stimulating factor ($n = 8$) and blood transfusion ($n = 1$). Of the patients presenting with haematological toxicity, 53.8% received concomitant CTx compared with 23.6% of patients treated without concomitant CTx.

Other Complications

Among 27 children with a ventriculoperitoneal shunt, four patients developed malfunctions. One patient presented with two subsequent malfunctions. Reasons were shunt blockage (CTCAE °IV), shunt infection (CTCAE °III) and local, inflammatory skin irritation (CTCAE °III). Shunt revision was required once ($n = 2$) or twice ($n = 1$) during the course of radiotherapy. Complications (mainly due to infections) with central venous catheters occurred in six patients (11.8%) (CTCAE °II, $n = 2$; CTCAE °III, $n = 4$). The proportion of patients with complications of the port catheter or central lines was 16.1% and 5.5%, respectively. A revision was required in four patients (7.8%). No complication associated with intraventricular devices was observed. Regarding nutrition support devices, one patient presented with peritubular skin inflammation (CTCAE °I). However, this patient did not require PEG replacement and management consisted of standard skin care.

Late Adverse Events

In three patients (5.8 %), a new ipsilateral hearing loss CTCAE °III was reported. Furthermore, 8% of the patients required hormone supplementation (growth hormone, $n = 3$; thyroid-stimulating hormone, $n = 1$) following radiotherapy. Additionally, one patient (1.9%) experienced visual impairment (CTCAE IV). Transient radiation-related imaging changes were seen in five patients (9.8%); four children without clinical symptoms and not requiring any kind of intervention. In one case with clinical symptoms, the clinical symptoms resolved completely after treatment with corticosteroids.

Hospital Admissions and Treatment Interruptions

Unplanned hospital admissions affected 12 patients. The duration ranged from 1 to 47 days (median 6 days). The reasons for hospitalisation were port catheter infections ($n = 5$; CTCAE °III), respiratory tract infections ($n = 4$; CTCAE °III), acute gastrointestinal infection ($n = 1$; CTCAE °II) and shunt malfunction ($n = 2$; CTCAE °IV). Treatment interruptions due to complications longer than 2 days occurred in five children (median 4, range 3–24). Of them, two experienced 11 or 24 days of treatment interruption (both due to ventriculoperitoneal shunt malfunction). In both children, no dose compensation was deemed feasible due to a total prescribed dose of already 59.4 Gy (RBE) in an infratentorial site close to the brainstem. In three patients, PBT was interrupted for 3–4 days due to fever.

Tumour Control and Overall Survival

The median follow-up time was 42 months (range 7.3–86.2 months).

For the entire cohort, the estimated 3-year local control, PFS and overall survival rates were 62.7, 47.1 and 76.5%, respectively (Figure 1). Of the 27 patients experiencing disease progression, 13 failed locally, eight developed dissemination and six had combined local and distant failure.

For the subgroup of ependymoma, the estimated 3-year local control, PFS and overall survival rates were 57.7, 46.2 and 92.3, respectively. Fourteen patients experienced tumour progression either due to local failure ($n = 9$), distant failure ($n = 3$), or combined local and distant failure ($n = 2$), respectively (Figure 2).

For the subgroup of patients with ATRT, the estimated 3-year local control, PFS and overall survival rates were 65.0, 40.0 and 50.0%, respectively. Twelve patients experienced progression, four of them developed local failure, five distant failure and three patients combined local and distant failure (Figure 3).

The pattern of relapse for metastatic patients is displayed in Table 4.

Discussion

Within this analysis, we report our institutional experience of PBT in 51 infants with brain tumours enrolled in a prospective in-house registry. Although there are a number of publications covering radiotherapy in infants, these only looked at a single tumour entity and focused on either toxicity or tumour control [3,7,12,23–36]. Larger cohorts were addressed by two retrospective SEER studies, but the analysis did not consider any details of radiotherapy treatment [2,37]. By contrast, our study is, to the best of our knowledge, the first not only to report toxicity and outcome of infants with brain tumours, but also medical challenges during the course of radiotherapy. Consistent with previous reports, our cohort was exposed to extensive multimodal treatment. Therefore, a relevant risk for complications has to be considered and radiotherapy may contribute negatively to the overall treatment burden. The substantial number of neurological impairments reported in 21/51 children before even starting radiotherapy reflects the burden of intensive local approaches and may potentially impact on the feasibility of radiotherapy. Therefore, understanding the individual risk profile seems to be essential. Additionally, high demands for optimal timing

and coordination of all treatment modalities have to be considered.

Our cohort predominantly comprised ependymoma and ATRT as radiotherapy for those is typically recommended, even at a very young age. This is particularly the case for tumour progression or in the presence of individual high-risk features.

The ACSN0121 study reported a 5-year PFS of 68.5% for patients with ependymoma younger than 3 years with gross total resection followed by immediate radiotherapy as compared with 37.2% after subtotal resection and radiotherapy [24]. In our cohort of patients with ependymoma, the estimated 3-year PFS was 46.2%, but GTR was achieved in only 53.8% of the patients. Consequently, we report reasonable results despite a rather high-risk cohort.

The estimated 3-year PFS rate for ATRT for our cohort was 42.2%, comparable with the findings from McGovern *et al.* [38] reporting a 2-year PFS of 47.6% in a cohort of 33 ATRT (median age 19 months) treated with PBT.

So far, little information has been provided on adverse events and complications when treating infants. In a series of 15 children with a median age of 18.9 months treated with PBT for ATRT, no CTCAE °II or greater acute toxicity was reported [35]. Similar results were reported [25] for children with infratentorial brain tumours under the age of 3 years. By contrast, we observed a relevant number of higher-grade adverse events when providing care for infants during irradiation. However, within our analysis the incidence of acute toxicity directly attributable to radiotherapy is consistent with Weber *et al.* [25]. However, different from the findings reported by Weber *et al.* [25] we revealed complications not directly caused by radiotherapy, but significantly contributing to the complexity of care. Our experiences reflect the significant challenges that come with concomitant CTx and various invasive devices. More patients with concomitant CTx experienced higher-grade haematological toxicity (53.8%) when compared with patients without CTx (23.6%). Although shunt malfunction was not common, it significantly compromised the condition of the affected patients. In both patients requiring shunt revision, subsequent treatment interruption of the radiotherapy course of 10 and 24 days occurred. Therefore, an interdisciplinary team with easy and fast access to neurosurgery is crucial for the treatment of infants. Furthermore, radiotherapy has to be delivered at experienced and specialised centres providing all logistics to manage unexpected complications. Infrastructures have to be appropriate to easily switch from outpatient to inpatient care on demand.

Our complication rate due to the central venous catheter compares favourably with the findings of Bratton *et al.* [39], who evaluated 170 patients aged between 1 and 10 years undergoing radiotherapy. Similar to our cohort, catheter insertion was used for CTx, anaesthesia or both. They reported a complication rate of 20.5% for central lines and 14% for port catheters. In comparison, 16.1% of our patients

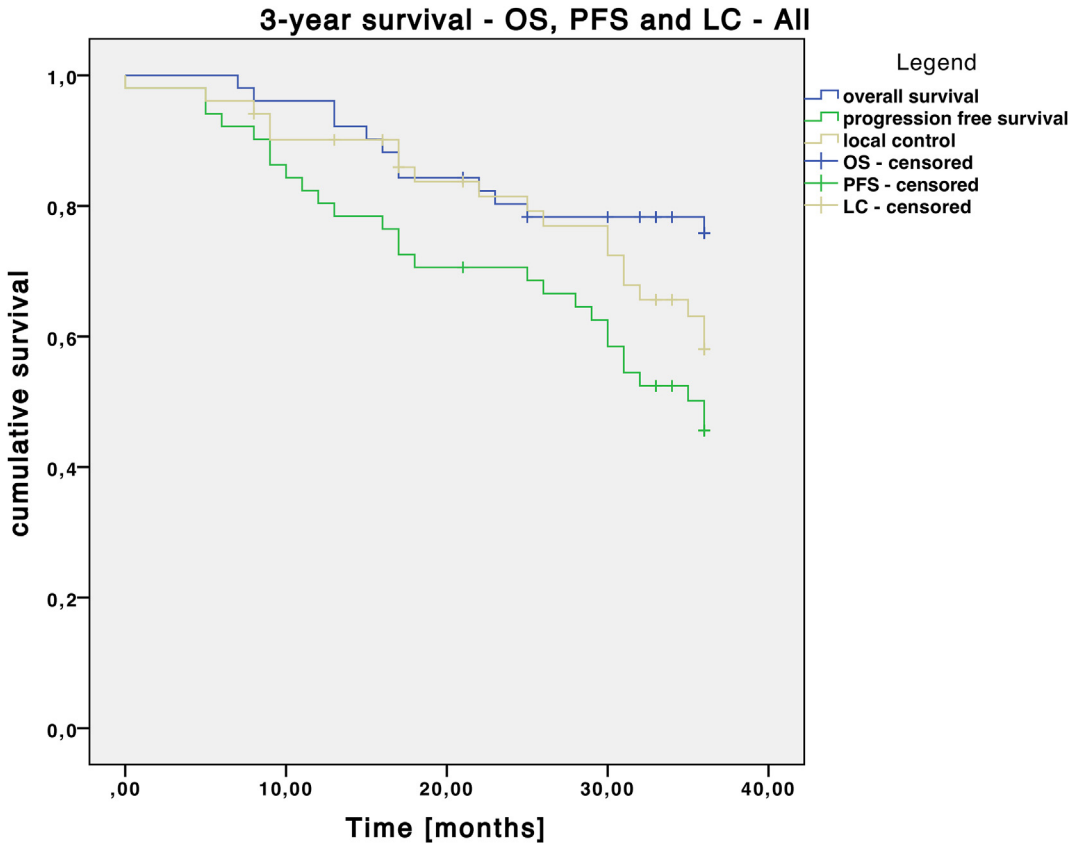

Fig 1. Kaplan-Meier estimates of the local control, progression-free survival and overall survival of all patients.

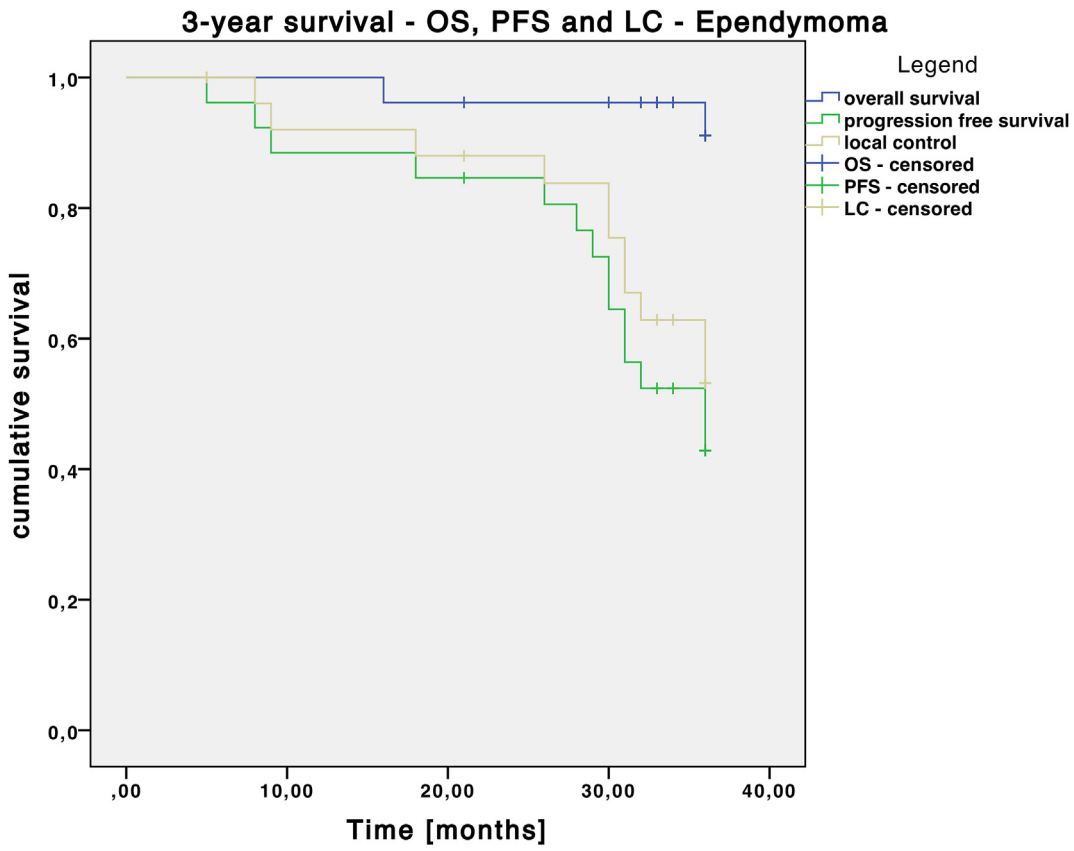

Fig 2. Kaplan-Meier estimates of the local control, progression-free survival and overall survival of patients with Ependymoma.

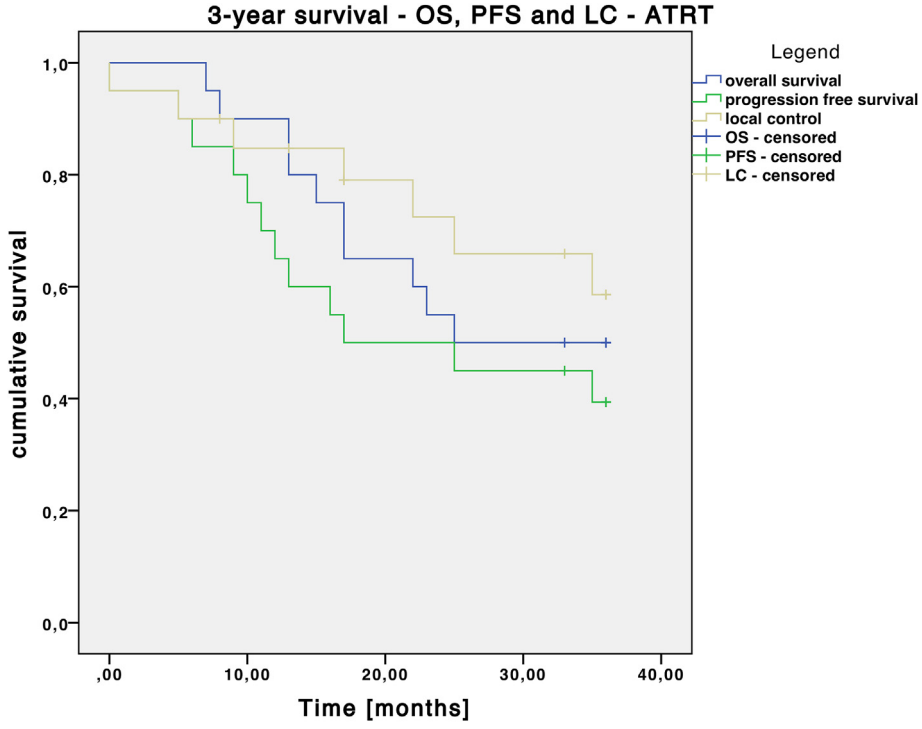

Fig 3. Kaplan-Meier estimates of the local control, progression-free survival and overall survival of patients with ATRT.

Table 4
Pattern of relapse for metastatic patients with regards to radiotherapy volume

	Diagnosis	M-stage	Target volume of radiotherapy	Local failure	Leptomeningeal failure
1	Ependymoma	M1	Local	No	No
2	Medulloblastoma	M1	CSI	No	No
3	ATRT	M1	CSI	Yes	Yes
4	ATRT	M1	Local	No	Yes
5	ATRT	M2	CSI	Yes	No
6	ATRT	M3	CSI	Yes	No

ATRT, atypical teratoid rhabdoid tumour; CSI, craniospinal irradiation; M0, no evidence of metastasis; M1, tumour cells identified by cerebrospinal fluid cytology; M2, intracranial metastatic tumour; M3, spinal metastatic tumour.

experienced port catheter complications and 5.5% experienced complications with their central lines. In addition, challenges may arise from PEG or nasogastric feeding. In our study, only one minor complication (CTCAE°I) was observed. Therefore, our study supports the consideration of PEG or nasogastric tube if any risk of malnutrition is foreseen [35].

With regards to late effects, sensorineural hearing loss can be a substantial complication experienced after cranial radiotherapy. Indelicato *et al.* [27] examined 179 paediatric patients receiving PBT with a median age of 3.5 years with ependymoma. The authors reported that 6.1% of the participants experienced hearing loss. Having a comparable follow-up time, our data are comparable. Of note, ototoxicity in all affected infants was anticipated in planning, as sparing of one cochlea seemed not advisable due to tumour localisation.

Data obtained in childhood cancer survivors imply that radiotherapy substantially contributed to endocrine complications [40]. As the dose of radiotherapy has shown a correlation with the risk of endocrine dysfunction [41], PBT is an attractive treatment modality. Investigators from the Massachusetts General Hospital reported an incidence of growth hormone and thyrotropin deficiency of 8% and 3.1%, respectively [42]. Additionally, the abovementioned study by Indelicato *et al.* [27] reported endocrinopathies in 7.3% of the cases. In our study, 8% of infants required hormone supplementation, which is comparable with previous publications on children treated with focal PBT.

There is an increased awareness of radiation necrosis as it can have a dramatic impact on the patient's well-being. PBT was discussed to carry an increased risk when compared with other radiotherapy modalities [43]. Therefore, imaging findings of MRI after PBT have to be reviewed carefully, particularly if going along with clinical symptoms. In our study, five patients (9.8%) presented with imaging changes following PBT. However, four were asymptomatic and resolved without any intervention. In the one symptomatic case, steroid therapy led to complete remission. This observation is in line with previous data. A series of 18 children younger than 3 years of age reported on imaging changes in eight cases [36]. All of them were transient. Indelicato *et al.* [27] reported a cumulative incidence of brainstem toxicity in children with ependymoma of 5.5%. However, McGovern *et al.* [38] published on 31 children with ATRT and revealed radiation reactions in the brainstem requiring bevacizumab or steroids in five patients. Although young children were suggested to be more susceptible to radiation necrosis [44], from our data, all findings were transient. Therefore, our data do not confirm any increased risk when compared with any radiotherapy data, even in a cohort with a median age of 19 months.

It has to be noted that the present study can only summarise preliminary experiences as the follow-up time was limited. In addition, neurocognitive outcome was not measured, which constitutes a crucial parameter when defining the role of radiotherapy in the very young.

Because of the limited number of patients included in this study, and the limited knowledge on the biology of each patient's tumour, no definite conclusions on the preliminary efficacy can be drawn. Furthermore, we acknowledge that no central imaging review was carried out.

In conclusion, our data revealed that treatment of infants with brain tumours is feasible with acceptable acute and late toxicities. However, optimal medical care is challenging, requiring a high multidisciplinary effort. Due to its high conformity, PBT can be advantageous to limit the risk for complications and it is increasingly used, particularly in very young patients. However, in very young children, radiotherapy has to be reserved for patients where cure can hardly be achieved when omitting radiotherapy. Future data have to prove whether the long-term benefits of an intensive multidisciplinary treatment strategy including radiotherapy can outweigh the risks for adverse events. Strategies for this sensitive cohort have to be established in the framework of international multidisciplinary trial groups.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgement

We would like to thank Professor Dr G. Fleischhack for continuous support and advise when individually tailoring challenging treatment concepts in children with brain tumours.

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