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Abstract

Background. Radiotherapy (RT) of ependymoma in children is an important part of the interdisciplinary treatment concept. However, feasibility and dose concepts are still under investigation, particularly in very young children. The aim of this study was to evaluate the standard dose and volume of proton therapy (PT) in children with ependymoma.

Methods. In this analysis, 105 patients with localized, intracranial ependymoma under the age of 18 years treated with PT between 2013 and 2018 were included. Patient characteristics, treatment, outcome, and follow-up data were analyzed using descriptive statistics, Kaplan-Meier, and Cox regression analysis.

Results. The median age of patients at PT was 2.8 years (0.9-17.0 years). The molecular subgroup analysis was performed in a subset of 50 patients (37 EP-PFA, 2 EP-PFB, 7 EP-RELA, 2 EP-YAP, 2 NEC [not elsewhere classified]). The median total dose was 59.4 Gy (54.0-62.0 Gy). The median follow-up time was 1.9 years. The estimated 3-year overall survival (OS), local control (LC), and progression-free survival (PFS) rates were 93.7%, 74.1%, and 55.6%, respectively. Within univariable analysis, female gender and lower dose had a positive impact on OS, whereas age ≥4 years had a negative impact on OS and PT given after progression had a negative impact on PFS. In the multivariable analysis, multiple tumor surgeries were associated with lower PFS. New ≥3° late toxicities occurred in 11 patients.

Conclusion. For children with localized ependymoma, PT was effective and well tolerable. Multiple surgeries showed a negative impact on PFS.

Key Points

- Estimated 3-year OS, 3-year LC, and 3-year PFS were 93.7%, 74.1%, and 55.6%.
- More than one tumor surgery significant risk factor for PFS.

Importance of the Study

This study represents the largest cohort of ependymoma patients (n = 105) treated with PT within Europe. Treatment standards as well as outcomes for the treatment of ependymoma in Europe's largest pediatric PT facility are presented here for the first time in detail. The cohort of our study forms a particular homogeneous group of patients since all patients have started their treatment within a 5.1-year period. In addition, data have been collected within the prospective KiProReg registry study. Furthermore, this study also includes detailed pathological aspects for a subgroup of PT patients. Due to the rareness of pediatric cancer, sharing outcomes is necessary to gain worldwide experience in order to improve patient treatment.

Ependymomas are one of the most common CNS tumors in childhood[1] presenting predominantly localized without metastasis at the time of diagnosis.[2] However, ideal treatment of non-metastatic ependymoma remains a matter of discussion. Further understanding of molecular subtypes has been gained in recent years, but the influence on treatment protocols is under debate.[3] Current optimal standard therapy includes complete surgery followed by adjuvant radiotherapy (RT). Due to the typically young age of patients, there is major concern about late effects. Due to the physical advantages of proton therapy (PT), an increasing number of pediatric patients are being treated with PT worldwide.[4]The role and ideal timing of chemotherapy is unclear and therefore currently a matter of clinical investigation.[5,6] Overall, the feasibility of therapeutic regimens with special regard to long-term adverse effects needs to guide treatment strategies for this group of young patients.

Regarding RT, doses that can be administered safely are limited by the tolerance of the normal tissue.This is critical, particularly in posterior fossa tumors in close proximity to the brainstem or extending into the spinal canal. Failures still occur typically locally within the tumor bed but also distant failures are of concern.[7] Potential benefit of higher doses for overall survival (OS) has been presented in a report of the American National Cancer Database.[8] In addition, strategies, including delay of RT or dose reduction for very young children, have recently been published with promising results.[9] Therefore, dose escalation remains a matter of investigation in childhood ependymoma.[9–11] Particularly in young patients the optimal dose to the tumor bed still needs to be defined. Our present study investigates our in-house standard approach, aiming to achieve both high local control (LC) rates and good feasibility for this particular vulnerable group of patients.

Clinical and biological prognostic factors for tumor outcome have been described in the literature. The extent of resection was understood to have the greatest impact on prognosis.[12–14] Additionally, male gender and young age were suspected to be associated with poor outcome. Besides these clinical risk factors, new molecular subgroups with different outcomes were identified.[3,15,16] Further examination of histopathological and molecular biological parameters aims to guide future risk stratification.[17,18] Additionally, a better understanding of MRI suggests new predictive markers for tumor recurrence.[19]

This evaluation of the largest group of ependymoma patients treated with PT within Europe enables comparison with international experiences and may help to determine international standards. Subgroup analysis may trigger further discussion on optimal RT.

Materials and Methods

All patients included in this analysis were enrolled in the prospective registry study "KiProReg" (German Clinical Trial Register: DRKS-ID: DRKS00005363) after formal consent from their legal guardian(s). This study was approved by the local ethics committee. Patients with non-metastatic intracranial ependymoma, graded WHO (World Health Organization) II/III, completely staged including MRI and lumbar puncture at diagnosis, receiving PT were included. Patients were excluded if they had received any prior RT, premature termination of PT, or missing follow-up (FU) data. Medical and treatment data were assessed in a standardized manner prior to and during treatment as well as at the defined FU time points according to the "KiProReg" registry study. For staging and diagnosis, cranial and spinal MRI prior to surgery and post-surgery MRI were obtained and cerebrospinal fluid was examined post-surgery. A number of tumor surgeries and a total number of cranial surgeries considering procedures for hygroma, hydrocephalus, bleeding, infection, or impaired wound healing prior to PT were documented. RT aftercare was scheduled after 3 months and annually thereafter. FU imaging was performed in accordance with the respective study protocols and the local standards of the referring pediatric hospitals, but always within 3 months of treatment and annually thereafter. Clinical side effects were recorded prior to PT, weekly during PT as well as at the aftercare appointments according to CTCAE Criteria 4.0.

With regard to PT, degraded beams of the 230 MeV cyclotron were used for patient treatment. Doses were expressed in Gy. For the calculation of the relative biological effectiveness, a factor of 1.1 as a relative to Cobalt 60 was used.[20] All doses in this manuscript are stated as Cobalt equivalent doses. PT planning included a 3-dimensional planning CT scan and MRI. Position was either prone or supine. Immobilization was assured by a thermoplastic mask and typically an additional vacuum mold. If patients were too young to consciously cooperate, sedation with i.v. propofol was provided by a pediatric anesthesiologist. If patients were included in national or international protocols, they were treated according to that respective protocol. Hypofractionated boosts were applied according to international study protocols. Patients not included in

any study were treated according to the in-house standard RT concept (Table 1) up to a total dose of 59.4 Gy or 54 Gy, respectively. Dose was limited to 54 Gy in very young children under 4 years, after multiple surgeries or in case of poor neurological status prior to PT and typically in the absence of residual disease. All patients received a radiation dose of 54 Gy (1.8 Gy/fraction) to the tumor bed plus margins for the clinical target volume (CTV) of 5-10 mm and another 3-5 mm for the planning target volume (PTV). Patients older than 4 years or younger ones with residual tumor received an additional boost of 5.4 Gy (1.8 Gy/fraction) to the tumor residue or to the tumor bed plus a PTV margin up to a cumulative total dose of 59.4 Gy. Spinal cord was to be excluded below C1 after 50.4 Gy. Dose constraint to the brainstem was 59.4 Gy D_{max} (dose maximum; XIO, D_{max} = D_0.01%, RayStation, D_{max} = D_0.01 ccm). In order to ensure a dose gradient from the brainstem surface to the inside of the brainstem, an auxiliary structure was drawn in the middle of the brainstem cross-section. The dose to this structure, called brainstem center, was restricted to a mean dose of 54 Gy. Proton beam techniques applied were pencil beam scanning (PBS) or uniform scanning (US). For contouring and planning, RayStation version 7 (RaySearch Laboratories, Stockholm, Sweden) or XIO for US plans were utilized.

Distribution and relationship of attributes were calculated and compared using cross tables and chi-square test. OS, PFS, and LC rates were estimated using the Kaplan-Meier method; 95% confidence intervals will be given. OS was defined as the time from the end of PT to death due to any cause or the date of the last FU used for censoring. Any disease progression was defined as treatment failure. PFS was defined as the time from the end of irradiation to evidence of any disease progression. For LC the event was defined as evidence of local recurrence or local progression only. Without event, death or the date of the last FU were used for censoring in LC and PFS, respectively. Univariate analysis was conducted to analyze the risk factors influencing OS, PFS, and LC. The log-rank test was used to test the differences in Kaplan-Meier curves stratified by specific variables. Cox regression was administered to calculate hazard ratios (HR) and confidence intervals (CI). A multivariate Cox regression was performed to evaluate multiple prognostic factors for PFS. Variable selection was guided by backward stepwise selection using the elimination criterion of a *P* value >0.1. Statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA) and R statistic software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between September 2013 and December 2018, 163 patients with ependymoma received PT at the West German Proton Therapy Center. One hundred five children with a localized ependymoma were identified as meeting the inclusion criteria of this study (Figure 1). Patients originated from 13 countries (Supplementary Table 5). Sixty patients were male. Median age at diagnosis was 2.5 years for male patients and 2.2 years for female patients, median age at the start of PT was 2.8 years for the whole cohort. Thirteen patients were younger than 18 months at the start of PT. Thirteen patients were treated with PT for salvage at recurrence or tumor progression and were predominantly younger than 4 years (11/13 p./84.6%). WHO grading was performed in all patients. In a subgroup of patients (n = 50), reference histopathology and additional molecular classification were available. Herein, out of 39 infratentorial tumors, 37 were classified as EP-PFA subtype, whereas 2 were EP-PFB subtype. Of 11 supratentorial tumors, 7 showed RELA fusions, 2 carried YAP fusion, and 2 were NEC (not elsewhere classified).

All patients received surgery prior to PT and GTR/NTR (gross total resection/near total resection) was achieved in 71.4% cases. Resection was examined by age (GTR/NTR ≥ 4 years, 79.4%; GTR/NTR < 4 years, 67.9% [n.s.]). Chemotherapy regimens prior to PT included combinations of vincristine, cyclophosphamide, carboplatin, etoposide, cisplatin, methotrexate, and valproic acid. The median time from diagnosis to the start of PT in patients without prior chemotherapy was 58 days (range, 23-246 days). If chemotherapy was administered prior to RT, median time span was 186 days (range, 83-975 days).

The median duration of the PT course was 44 days (range, 39-78 days). PT had to be interrupted for more than 10 days in 3 patients due to urgent shunt revision. In 2 of these patients, fractions were added for compensation with cumulative doses of 57.6 Gy and 59.4 Gy, respectively. The median total dose of PT was 59.4 Gy (range, 54.0-62.0). Two patients received a boost of 8 Gy in two fractions to the residual tumor (cumulative total dose 62 Gy). The majority of

Table 1 In-House RT Concept for Ependymoma Patients With Regard to Patient Age

Target Volume	Patients >4 Years	Patients <4 Years
GTV1	Initial tumor	Initial tumor
GTV2	Residual tumor after surgery at the time of RT	Residual tumor after surgery at the time of RT
Tumor bed	Tumor cavity after surgery, eg, including GTV2	Tumor cavity after surgery, eg, including GTV2
CTV1	Tumor bed + 5-10 mm considering anatomical borders	Tumor bed + 5-10 mm considering anatomical borders
PTV1	CTV1 + 3-5 mm PTV margin	CTV1 + 3-5 mm PTV margin
PTV2	Tumor bed + 3-5 mm PTV margin	GTV2 + 3-5 mm PTV margin

Abbreviations: CTV, clinical target volume; GTV, gross tumor volume; PTV, planning target volume; RT, radiotherapy.

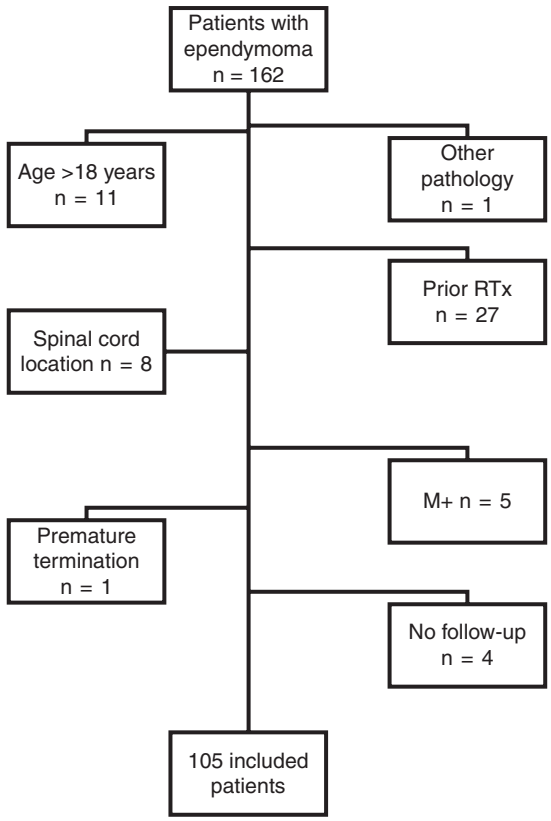

Fig. 1 Assessment of eligibility.

patients were treated according to the in-house standard, which was used for all patients not being the subject of a clinical trial. For patients being enrolled in other trials or registries, such as HIT MED-Registry, SIOP ependymoma II, or COG ACNS 0121, RT was performed according to the respective protocol. If necessary, treatment was individualized due to medical issues. Nine patients received chemotherapy concomitant to PT with weekly vincristine. One patient received 2 concomitant courses of vinblastine for ongoing treatment of Langerhans cell histiocytosis, which was diagnosed prior to the ependymoma. Details of patient and treatment characteristics are shown in Table 2 and Supplementary Table 6.

For the whole cohort, the median FU since the end of PT was 1.9 years (range 0.2-5.0 years) and since diagnosis 2.5 years (range 0.5-6.2 years). Until last FU, 6 children were deceased. All of them died of disease progression (dissemination, n = 5; local recurrence, n = 1). Recurrent disease occurred in 37 patients at a median time of 10.1 months (range 1.4-37.4). Sites of the first recurrence were local (n = 20), metastatic (n = 14), or both (n = 3). For the subgroup of patients treated with salvage, PT metastasis occurred as the first site of recurrence in 2 patients (15.4%) compared to 12 patients (13.0%) treated immediately. For the entire cohort, the estimated 3-year OS and PFS were 93.7% and 55.6%. The estimated 3-year LC rate was 74.1% (Figure 2; Supplementary Table 7). Age-specific survival data are shown in Supplementary Tables 8 and 9. Survival data were examined regarding dose and resection status in univariable analysis (Table 3).

Table 2 Patient Characteristics

Characteristics	N (%/range)
Gender	
Male	60 (57.1%)
Female	45 (42.9%)
Median age at diagnosis (years)	2.5 (0.1-16.9)
Median age at the start of PT (years)	2.8 (0.9-17.0)
WHO grade	
II	26 (24.8%)
III	79 (75.2%)
Tumor site	
Supratentorial	19 (18.1%)
Infratentorial	86 (81.9%)
Resection status	
GTR/NTR	75 (71.4%)
STR	30 (28.6%)
Median number of tumor surgery prior to PT	1 (1-4)
Median number of cranial surgery prior to PT	2 (1-10)
Timing of proton therapy	
At first diagnosis	92 (87.6%)
At recurrence/progression, salvage	13 (12.4%)
Prior chemotherapy	45 (42.9%)
Concomitant chemotherapy	10 (9.5%)
Sedation during PT	86 (81.9%)
PT technique	
PBS	59 (56.2%)
US	39 (37.1%)
PBS and US	7 (6.7%)
Treatment according to in-house standard	85 (81.0%)
Median total dose (Gy)	59.4 (54.0-62.0)
Median number of fractions	32 (30-33)
Stereotactic boost	2 (1.9%)
Median interval diagnosis to PT start (days)	102 (23-975)
Interruption of treatment >2 days	8 (7.8%)
Median FU since PT (years)	1.9 (0.2-5.0)

Abbreviations: FU, follow-up; GTR, gross total resection; NTR, near total resection; PBS, pencil beam scanning; PT, proton therapy; STR, subtotal resection; US, uniform scanning.

For the 50 patients with additional information on molecular biology, a separate analysis was performed. In patients with PFA, the median age at diagnosis was 2.4 years (range, 0.4-15.1), 2 patients with PFB were 9.8 and 13.3 years old. For patients with RELA fusions, the median age was 3.8 years (range, 1.5-11.9). The 2 patients with YAP fusions were 1.1 and 1.2 years and the 2 patients, NEC were 10.8 and 14.8 years of age, respectively. Recurrence or progression of disease occurred in 14 of these 50 patients

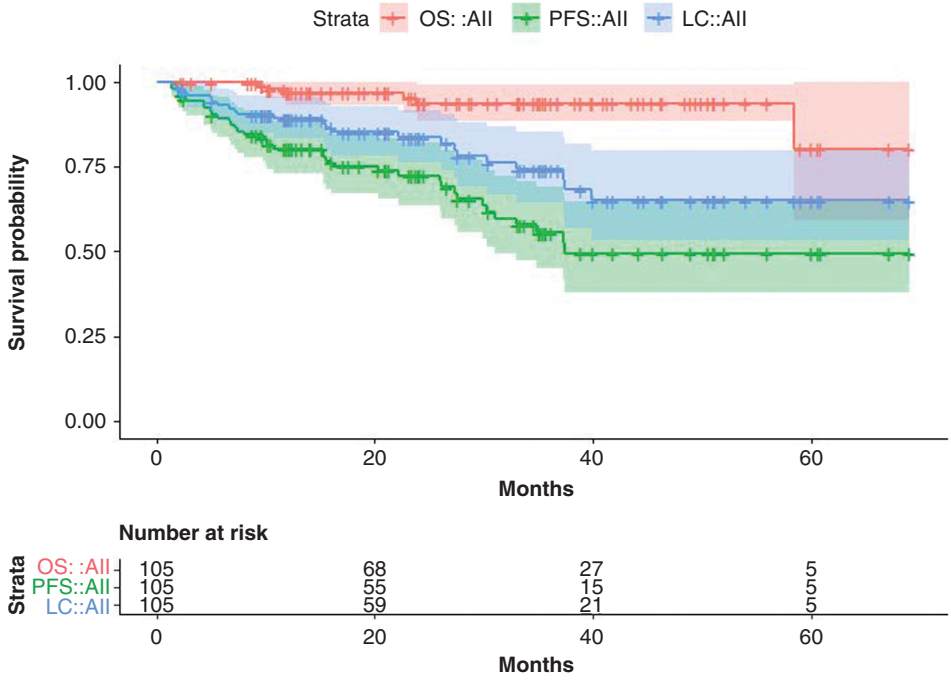

Fig. 2 Kaplan-Meier survival plot of estimated 3-year overall survival, progression-free survival, and local control with 95% confidence interval for the entire cohort.

(PFA, n = 10; YAP, n = 2; RELA, n = 2). Sites of the first recurrence were local (PFA, n = 4; YAP, n = 2), metastatic (PFA, n = 5; RELA, n = 1), or both (PFA, n = 1; RELA, n = 1). Neither in the PFB patients, nor in the two supratentorial ependymoma, NEC did tumor progression occur. Both patients with YAP mutation have so far remained alive despite experiencing local relapse. For patients with PFA, 3-year LC, PFS, and OS were 81.7% (95% CI 66.8%-96.6%), 66.6% (95% CI 49.0%-84.2%), and 91.1% (95% CI 82.1%-100%), respectively.

Univariate log-rank analysis for risk factors was performed for the entire cohort. An inferior PFS rate for patients with more than one tumor surgery prior to PT (P = .009/HR = 2.32) and patients receiving PT for salvage therapy (P = .046/HR = 2.41) (Table 4) were revealed. Female gender was associated with an inferior LC rate (P = .022/HR = 2.59). An inferior OS rate was found for patients with an age ≥4 years at the start of PT (P = .013/HR = 9.35). Patients receiving less than 59 Gy (P =.029/HR = 0.02) and female gender had a superior OS (P = .044/HR = 0.021). In the multivariable Cox regression model considering age, dose, extension of resection, WHO grade, and treatment according to in-house standard, only multiple tumor surgeries remained statistically significant (Supplementary Table 10). For the subgroup of patients with PFA subtype, univariate log-rank analysis was performed for resection status with an estimated 3-year PFS of 79.1% in GTR/NTR and 50.0% in subtotal resection (STR) (P = .108/HR = 0.369).

With regard to acute toxicity, new higher-grade acute toxicities CTCAE ≥3° occurred in 9 patients. It concerned (leukopenia, n = 3; anemia, n = 2; fever, n = 1; hydrocephalus, n = 1; hygroma, n = 1; agitation, n = 1; hearing impairment, n = 1; and anorexia, n = 1). With regard to late adverse events, new higher grade toxicities CTCAE ≥3° occurred in 11 patients. It concerned skin (n = 1), fatigue (n = 1), anemia (n = 1), anxiety/depression (n = 2), hearing impairment (n = 4), and optic nerve disorder.[2] Two patients with infratentorial tumor site, treated with 54 Gy (PBS), developed transient symptomatic changes on MRI (grade 2 according to Fouladi et al[21]) in T2 and with contrast enhancement 3.4 and 4.5 months after primary PT but regressing after steroid treatment. Changes occurred in the cerebellum and brainstem, respectively.

Discussion

This study represents the largest single-institution cohort of patients with ependymoma treated with PT in Europe. The characteristics of our patient cohort are comparable to other studies with a low median age and predominantly male patients.[7,9,22] In general, reported 3-, 5-, and 7-year OS rates of recent publications ranged between 90.4%-95%,[9,23] 70%-84%,[7,15,22,24] and 82.2%,[25] respectively. These results are comparable to the OS rate within our study. Recent studies of Patteson et al and Indelicato et al presented high 7-year PFS of 63.4% and 63.8%. In comparison to our cohort, the median age at RT was higher (Patteson et al, 3.6 years [0.3-20.9]; Indelicato et al, 3.8 years [0.7-21.3] vs our cohort 2.8 years [0.9-17.0]) and the percentage of male patients was lower (54% vs 55.96% vs 57.1%).[11,25] These

Table 3 Univariate Analysis of Dose for Estimated Progression-Free Survival, Overall Survival, and Local Control According to Status of Resection

Status of Resection	Dose (n)	E. 3-y PFS (%)	*P*	HR	95% CI	E. 3-y LC (%)	*P*	HR	95% CI	E. 3-y OS (%)	*P*	HR	95% CI
GTR/NTR (n = 75)	≥59 Gy (33)	66.9	.449	0.714	0.299-1.706	75.3	.733	0.823	0.269-2.521	96.6	.599	76.185	0-787 325 107.9
	<59 Gy (42)	47.6				76.3				100			
STR (n = 30)	≥59 Gy (22)	43.0	.51	1.531	0.431-5.443	66.0	.772	0.819	0.211-3.174	78.5	.476	32.078	0.002-444 217.796
	<59 Gy (8)	75.0				75.0				100			

Abbreviations: CI, confidence interval; GTR, gross total resection; HR, hazard ratio; LC, local control; NTR, near total resection; OS, overall survival; PFS, progression-free survival; STR, subtotal resection.

attributes might contribute to less favorable outcomes. Consistent with other reports, the most common form of relapse was local.[11,24,26] Still, in our cohort, metastatic dissemination as the first site of progression was more common than in previous studies.[22,27] However, Indelicato et al found metastasis to be the predominant type of failure in his cohort.[9] Our cohort contained patients treated after disease progression, but metastasis as the first site of recurrence was similar compared to the rest of the cohort. Gender has been discussed as a potential risk factor in several studies. Male gender has been associated with poorer outcomes in some publications,[9,22,28] while others have not identified gender as a significant risk factor.[15] According to our findings, male gender was associated with an inferior OS rate within univariate analysis. However, in contrast to other reports,[9,29] male gender was correlated with a significantly superior LC in our study. Age distribution between genders was similar.

Another risk factor discussed in literature was young age[13,15,30] and its distinct pathological pattern.[31] In our study, age lower than 4 years at PT start was associated with a significantly higher OS, even when the majority of younger patients received only 54 Gy. Significant differences in LC and PFS were not found. The extent of resection was similar between patients younger and older than 4 years. Because subtypes of ependymoma remain unknown for more than half of the cohort, disproportional distribution of subtypes with poorer prognosis could be an explanation for the inferior performance of the older age group. However, like us, De et al reported a similar pattern of outcomes with a significant superior 5-year OS in children younger than 5 years at diagnosis but without significant differences regarding PFS.[15]

Recent studies have found molecular subtypes to be a powerful prognostic factor regarding the outcome in ependymoma patients. Inferior prognosis has been associated with PFA subtype in posterior fossa tumors and RELA subtype in supratentorial location.[15,30,32] In literature, PFS data for posterior fossa tumors range between 5-year PFS rates of 24.0%-58.8% for PFA subtype and 5-year PFS rates of 73.0%-92.0% for PFB subtype.[3,30,32,33] In our cohort, additional histological data from the histopathological reference center were available for a subgroup of 50 patients. All of these patients were primarily treated in Germany or Austria. Due to the small sample size and the unequal distribution of subtypes, further statistical analysis to compare molecular subtypes and further evaluate risk factors was limited. In literature, PFA subtype was understood to be associated with younger patient age.[33] Further analysis of the outcome of patients with PFA subtype by Ramaswamy et al demonstrated PFA to be a risk factor independent of age at diagnosis. STR was found to be a significant risk factor for PFS in patients with PFA subtype in 3 of the examined cohorts.[30] In our study, we could confirm the relatively young age of PFA patients. Regarding resection status, the estimated 3-year PFS was higher for patients with PFA subtype if having had GTR/NTR. However, the difference failed to be statistically significant. For supratentorial location, YAP subtype is known to be associated with a superior outcome in literature with 5-year PFS of 66% and OS of 100%, see Pajtler et al.[3] In addition, Andreiuolo et al presented a group of 15 patients with YAP-1 subtype of which 14 patients had no tumor progression with a median FU time 4.82 years, while 1 passed away during surgery.[16] In contrast, in our study both patients with YAP subtype experienced early progression. Still, due to the limited number of patients, our data have to be interpreted with caution. Pajtler et al showed an inferior 5-year PFS and OS for RELA-fused supratentorial ependymomas.[3] Also, in our study, 2 out of 7 RELA patients experienced treatment failure, suggesting an unfavorable prognosis for this subgroup.

Our results are comparable to recently reported data. However, interpretation is difficult due to the small subgroup with molecular data available. Still, deeper understanding of molecular biological subtypes is necessary. In addition, the influence of chemotherapy remains a matter of investigation.[5,6]

Multiple tumor surgeries were identified as a risk factor in our evaluation. Patients with more than one tumor surgery had a significantly lower PFS within univariate and multivariable analysis. This is similar to the findings of Merchant et al, who reported a borderline significance for a number of tumor surgeries.[27] Complete resection can be challenging. However, multiple resections were generally attempted to reach GTR because resection status was recognized to have an important impact on outcome. In fact, residual disease was associated with higher local failure rates in various previous studies.[7,9,11,23,34,35] In the study of De et al, GTR was found to be a significant advantage for OS in multivariable analysis in the subgroup of patients treated prior to relapse.[15] Other studies failed to prove extension of resection being a prognostic factor.[36]

Table 4 Univariate Analysis of Risk Factors for Estimated Progression-Free Survival, Overall Survival, and Local Control

Variable	3-y PFS (%)	*P*	HR	95% CI	3-y LC (%)	*P*	HR	95% CI	3-y OS (%)	*P*	HR	95% CI
Gender												
Male (referent)	57.8				81.1				89.3			
Female	51.9	.734	1.12	0.583-2.150	65.0	.022	2.59	1.116-6.014	100.00	.044	0.02	0.000-18.520
Age at PT (years)												
<4 (referent)	51.4				69.5				98.3			
≥4 y	62.7	.499	0.78	0.386-1.592	82,5	.312	0.62	0.244-1.579	85.2	.013	9.35	1.089-80.309
Resection status												
GTR/NTR (referent)	55.9				75.8				98.6			
STR	51.4	.126	1.68	0.865-3.256	68.8	.127	1.90	0.832-4.358	83.6	.089	4.03	0.718-22.619
Prior CTX												
No (referent)	58.2				79.6				92.2			
Yes	52.8	.466	1.27	0.666-2.424	67.0	.078	2.13	0.920-4.923	96.3	.120	0.20	0.023-1.822
More than one tumor surgery												
No (referent)	64.7				77.5				96.1			
Yes	39.1	.009	2.32	1.217-4.429	67.5	.083	2.03	0.895-4.610	88.9	.21	2.98	0.497-17.817
WHO grade												
II (referent)	60.5				76.4				95.2			
III	54.3	.266	1.64	0.681-3.922	73.4	.199	2.17	0.646-7.323	93.5	.415	0.498	0.090-2.748
Location												
Supratentorial (referent)	59.9				68.4				100.0			
Infratentorial	53.9	.907	0.95	0.417-2.175	74.9	.287	0.61	0.238-1.541	92.4	.264	26.95	0.003-259 010.042
Time to PT (days)												
≤90 (referent)	56.6				76.4				94.3			
>90	55.4	.817	1.08	0.563-2.074	72.2	.586	1.26	0.545-2.925	93.2	.722	0.75	0.148-3.758
Dose (Gy)												
≥59 (referent)	57.2				72.2				88.0			
<59	53.5	.903	0.96	0.501-1.840	76.5	.973	1.01	0.447-2.304	100.0	.029	0.02	0.000-16.598
Timing of PT												
At first diagnosis (referent)	58.4				74.6				94.8			
Recurrence/progression	27.5	.046	2.41	0.988-5.870	74.0	.178	2.07	0.702-6.102	80.0	.425	2.38	0.265-21.270
Treatment according to in-house standard												
No (referent)	61.8				74.3				91.7			
Yes	53.7	.366	1.50	0.621-3.604	74.1	.995	1.00	0.370-2.721	94.2	.685	1.57	0.177-13.982

Abbreviations: CI, confidence interval; CTX, chemotherapy; GTR, gross total resection; HR, hazard ratio; LC, local control; NTR, near total resection; OS, overall survival; PFS, progression-free survival; PT, proton therapy; STR, subtotal resection.

In univariate analysis, we could confirm GTR/NTR to be neither a significant good prognostic factor for PFS for the whole cohort nor for the subgroup treated prior to relapse. Univariate analysis demonstrated a significant difference between GTR/NTR and STR for patients treated after relapse in our cohort regarding OS ($P = .046$). Results may be limited due to the small size of subgroups. Ramaswamy et al discussed STR as a risk factor in the PFA subgroup.[30] It seems that at least some subgroups of ependymoma patients might benefit significantly from GTR. Further specifying these subgroups will be important in order to outweigh risks of aggressive surgery and survival benefits.

RT is an important backbone of treating ependymoma even in children of very young age. This is shown by the data of HIT-SKK'87 and HIT-SKK'92.[37] Even if in general promising OS rates were achieved, the optimal total dose of radiation is still under investigation in international trials such as the SIOP ependymoma II trial.[5] High local tumor control and survival rates have been achieved with regimens of fractionated RT up to 54-59.4 Gy. Within the SIOP ependymoma II trial, even cumulative doses of 67.4 Gy are prescribed in patients with tumor residue at the time of RT. However, concerns about feasibility remain, particularly regarding very young children, after multiple

surgeries or patients with neurological impairments.[10,15] Therefore, it is an open question for whom doses can be limited to 54 Gy in order to best balance treatment intensity in this vulnerable group of patients.[27,38] According to our findings, no significant difference regarding LC and PFS between patients receiving radiation doses lower or higher than 59 Gy was observed within univariate analysis. Concerning the OS, patients receiving less than 59 Gy had a significantly better estimated 3-year OS in univariate analysis. However, we have to bear in mind that higher doses were reserved for patients with risk factors. In a subgroup analysis of patients younger than 4 years of age, LC, PFS, and OS were higher in the group receiving less than 59 Gy but failed to be significant. In this younger subgroup, patients who received a lower radiation dose predominantly had GTR/NTR (82.6%). If patients with STR received less than 59 Gy, a dose higher than 54 Gy was typically not considered feasible due to neurological issues. Therefore, dose reduction to 54 Gy in this selected subgroup of younger patients seems to achieve satisfying results. Treatment according to in-house standard was evaluated in univariate analysis for respective outcomes, which were similar to those of other patients. These data support good outcome with doses of 54 Gy in this particularly young subgroup. Also, in an earlier study by Merchant et al with predominantly younger patients receiving 54 Gy, no difference in local failure rates by total dose was found. This is in accordance with the recent study of Patteson et al not showing a significant influence of radiation dose on LC. In accordance, several other studies could not demonstrate a significant benefit of higher radiation dose.[9,11,15,39] In a study by Indelicato et al, higher doses were not associated with a higher LC, even when stratified for resection status. We did confirm these findings. Furthermore, we could not reveal any significant impact of dose on OS and PFS for higher dose and STR. Also for GTR/NTR, dose did not show any significant influence on LC, PFS, and OS. Nevertheless, we have to acknowledge that interpretation is difficult due to the small size of these subgroups and unequal distributions of possible risk factors such as age, gender, pathology, or treatment at recurrence. In contrast to these findings, a retrospective study of ependymoma patients in France by Tensaouti et al showed a significantly higher local failure rate in patients treated with only 54 Gy or less.[7] Also, in other studies, higher radiation dose was a prognostic factor.[8,40] Comparability to our cohort is limited by differences in age, extend of resection, and proportion of higher graded tumors.

PT was not associated with any significant acute toxicities in the majority of patients. Bone marrow suppression was mainly associated with concurrent or prior chemotherapy. A new hydrocephalus occurred due to malfunction of a ventricular shunt device and required neurosurgical treatment. Likewise, the patient with hygroma. Agitation was developed by 1 patient within 3 months after therapy but resolved later. One patient developed anorexia within 3 months after treatment but was later newly diagnosed with Crohn's disease which most likely caused the anorexia.

Regarding long-term side effects, 2 patients were diagnosed with vision impairment on one side after 1 and 3 years without signs of recurrence or radionecrosis. Both patients had presented infratentorial tumor at the time of first diagnoses and were at that time too young to perform reliable ophthalmological testing prior to RT. However, both patients presented optical disturbances like diplopia, paresis of N. trochlearis, and ptosis prior to radiation treatment. D_{max} to the optical nerve was only 30.63 and 29.41 Gy making association with radiation unlikely. Four patients with infratentorial tumor side developed hearing impairment grade 3 in one ear between 1 and 4 years after PT. Doses to the cochlea were above dose constraint as tumor extension involved the internal acoustic canal. All of these patients received CTX prior to PT (2 also concomitantly).

Symptomatic radionecrosis after RT in ependymoma patients has been reported throughout the literature. Sato et al report 5 out of 79 patients with necessity for steroid treatment.[41] In a cohort of Merchant et al, 2 in 153 children developed a necrosis requiring treatment.[27] Other studies present brainstem toxicities at a rate of 5.5% and hearing loss at a rate of 6.1%.[9] Ares et al reported one fatal brainstem necrosis.[22] In our cohort, the rate of symptomatic radiation-induced changes is in line with previously published data. The transient character of findings is worth noticing. Additionally, the low rate of new grade 3 toxicities supports the good feasibility of this treatment.

Limitations of our study include small size of subgroups, limited observation time, and different treatment strategies. In addition, it would be desirable to have specification of subtypes for all patients.

Conclusion

To apply optimal dose concepts in a vulnerable patient group, both under- or overtreatment have to be avoided. Therefore, RT has to be adjusted to the individual risk profile. Our data support the hypothesis that dose limitations can result in high tumor control for selected groups of patients. Keeping in mind the sensitive age of ependymoma patients and neurological challenges after surgery, our treatment standard seems to provide a safe approach with results comparable to international experiences. In future, further investigation of risk factors and tumor genetics is a promising approach for individual risk assessment and novel clinical risk-adapted treatment strategies. Locally intensified treatment regimens should remain part of international trials such as SIOP ependymoma II.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

Keywords

childhood | ependymoma | molecular subtype | proton therapy | radiotherapy

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