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ORIGINAL ARTICLE

Outcome of postoperative radiation therapy for pediatric intracranial ependymoma: a single-institution review

Rawee Ruangkanchanasetr[1] · Thiti Swangsilpa[1] · Putipun Puataweepong[1] · Mantana Dhanachai[1] · Ake Hansasuta[2] · Atthaporn Boongird[2] · Nongnuch Sirachainan[3] · Suradej Hongeng[3]

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Abstract

Purpose To report outcome of postoperative radiotherapy (RT) in both new and recurrent grade II and III intracranial ependymomas in children treated at Ramathibodi Hospital.

Materials and methods Between 2006 and 2017, 24 pediatric intracranial ependymomas treated with postoperative RT were retrospectively reviewed. The median age at diagnosis was 44.5 months (range, 4–165 months). There were 14 (58%) males. Fourteen (58%) patients had infratentorial tumor. The median maximal diameter of tumor at diagnosis was 4.45 cm (range, 2.2–10 cm). Fourteen (58%) patients had anaplastic tumor. Gross total resections were performed in 14 (58%) patients. The median prescribed dose was 54 Gy (range, 45–60 Gy). The median total treatment time was 43 days (range, 37–78 days).

Results The median clinical follow-up time was 44.5 months (range, 1–146 months). There were nine recurrences, five of which occurred at the primary tumor site. The estimated 5-year progression-free survival rate was 56%. The estimated 5-year overall survival rate was 75%. Extent of resection was the only factor associated with improved progression-free survival and overall survival after univariate testing. Six from nine patients with recurrent diseases underwent further surgery or further RT. These six patients had better median overall survival than the three who did not. Acute complication was mostly transient and tolerable. No late radiation effect was found.

Conclusions Postoperative radiation is an effective treatment. GTR is associated with better PFS and OS. Aggressive salvage local treatments for recurrent patients can result in good overall survival. Longer follow-up is needed in account for late relapse.

Keywords Ependymoma · Intracranial · Pediatrics · Radiotherapy

Introduction

Ependymomas are one of the few types of pediatric brain tumor occurring, accounting for 7% of all primary childhood brain tumors occurring in the USA [1]. Their treatment differs to that of other pediatric brain tumors, as chemotherapy has only a limited effect. Maximum safety resection is the mainstay of treatment, with it usually being followed by postoperative radiation therapy (RT) in grade II and III intracranial ependymomas, to reduce the local recurrence.

The treatment of ependymoma has seen many developments over the past 20 years. The improved quality of radiological imaging helps to define the tumor's extension more accurately, while new surgical techniques allow more aggressive tumor resection without a higher rate of severe neurological deficit. There have also been many developments in RT, such as new techniques for RT delivery, and a reduction in the size of RT fields allow us to give a higher dose of radiation,

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✉ Rawee Ruangkanchanasetr
rawee.rua@mahidol.ac.th

✉ Suradej Hongeng
suradej.hon@mahidol.ac.th

[1] Radiation and Oncology Unit, Department of Diagnostic and Therapeutic Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand

[2] Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand

[3] Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand

thereby improving local tumor control, while also limiting the dose to normal tissue to avoid the severe RT side effects [2].

The objectives of this study were to report the long-term outcomes of postoperative RT for both new and recurrent intracranial ependymomas in children treated at Ramathibodi Hospital, Thailand, and to further identify factors affecting these outcomes.

Material and methods

Patients

This retrospective study was approved by our institutional ethics committee. The eligibility criteria for the study included (1) pediatric patients with pathologically confirmed grade II or III intracranial ependymoma, (2) patients who underwent maximum safety resection, and (3) patients who received curative postoperative radiation therapy in Ramathibodi Hospital. Between 2006 and 2017, 24 pediatric patients were eligible for this study. Details of the patient and tumor characteristics are shown in Table 1.

Surgery

Surgery was performed as the primary treatment in all patients. The number and extent of surgeries are presented in Table 1. Salvage surgery was considered if there was tumor progression or gross residual tumor after RT had been completed.

Chemotherapy

Six patients (28%) received chemotherapy prior to radiation, with 83% of these patients being aged less than 36 months. One patient received a vincristine/carboplatin protocol, while the other five patients received alternating vincristine/cyclophosphamide, vincristine/methotrexate, and carboplatin/etoposide protocols. Three patients (50%) had progressive disease after neoadjuvant chemotherapy. The median time to chemotherapy failure was 9 months.

Radiotherapy

The RT technique, treatment volume, and radiation dose were based mainly on physician preference and the time era when the patient was treated. In the earlier part of the period covered by the study, two patients were treated with a Cobalt-60 machine (Theratron Elite80; MDS Canada Inc., Kanata, Canada). However, in 2007, we began using a Varian 2100C linear accelerator (Palo Alto, CA, USA), which was later replaced with a Varian Clinac IX machine (Palo Alto, CA, USA) in 2010. More advanced radiation techniques such as three-

Table 1 Patient, tumor, and treatment characteristics of the 24 patients in this study

Sex, no. (%)	
Male	14 (58)
Female	10 (42)
Median age at diagnosis, months (range)	44.5 (4–165)
Median age at RT, months (range)	51.5 (22–167)
Age at RT, no. (%)	
< 3 years	5 (21)
≥ 3 years	19 (79)
Recurrent tumor, no. (%)	
Yes	5 (21)
No	19 (79)
Grading, no. (%)	
II	10 (42)
III	14 (58)
Location of tumor, no. (%)	
Infratentorial	14 (58)
Supratentorial	10 (42)
Median tumor diameter, cm (range)	4.45 (2.2–10)
Spinal metastasis, no. (%)	
Yes	4 (17)
No	16 (66)
Not done	4 (17)
Number of surgeries performed prior to RT, no. (%)	
1 time	15 (63)
2 times	5 (20)
3 times	4 (17)
Extent of surgery, no. (%)	
Gross tumor removal	14 (58)
Partial tumor removal	9 (38)
Biopsy	1 (4)
Neoadjuvant chemotherapy, no. (%)	
Yes	6 (25)
No	18 (75)
RT volume, no. (%)	
Local field	16 (66)
Wide field	3 (13)
CSI	5 (21)
RT technique, no. (%)	
2D	1 (4)
3D	16 (66)
IMRT	4 (17)
Mixed 3D + IMRT	3 (13)
Median total dose at primary site, Gy (range)	54 (45–60)
Total dose to primary site, no. (%)	
< 54 Gy	8 (33)
≥ 54 Gy	16 (67)
Median total treatment time, days (range)	43 (37–78)
Total treatment time, no (%)	
< 50 days	17 (71)
≥ 50 days	7 (29)

Table 2 Characteristic, treatment, and outcome data for each patient

Pt	Age (mo)	Sex	M+	GTR	NAC	Field of RT	RT dose (Gy)	Final disease status after RT	PFS (mo)	Pattern of failure	Recur (times)	Salvage treatment			Clinical F/U (mo)	Death	TTD (mo)	Final disease status at latest F/U
												Surgery (times)	RS/RT (times)	CMT (courses)				
1	33	M	Y	Y		CSI	54	NED	146						146			NED
2	34	M		Y		Local	50.4	NED	138						138			NED
3	68	M	Y	Y		CSI	50	PD	97	Local	3	3			128			NED
4	84	F				Local	50.4	PD	35	Local	4	4	2		72	Y	79	PD
5	74	M	Y	Y		CSI	59.4	NED	47						47			NED
6	52	M		Y		Wide	54	NED	110						110			NED
7	14	F			Y	CSI	55	PD	1	Combined	1				4	Y	18	PD
8	32	M	Y		Y	CSI	45	PD	13	LMM	1			1	42	Y	45	PD
9	30	M		Y		Local	54	NED	82						82			NED
10	165	M				Local	55.8	PD	58	Local	1		1		77			SD
11	94	F				Local	55.8	SD	60						60			NED
12	145	F	NA	Y		Wide	59.4	NED	56						56			NED
13	4	F	NA		Y	Local	54	SD	1						1	Y	33	SD
14	44	F				Local	60	PD	1	Combined	1	1			12	Y	17	PD
15	31	F		Y	Y	Local	50	NED	35						35			NED
16	11	M	NA	Y	Y	Local	50.4	PD	30	Local	1	1			35			NED
17	42	M	NA	Y		Local	54	NED	50						50			NED
18	127	F		Y		Local	50.4	NED	4						4			NED
19	22	F		Y	Y	Wide	59.4	NED	5						5			NED
20	57	M				Local	59.4	PD	9	LMM	1	1	1		27			PD
21	47	M		Y		Local	54	NED	25						25			NED
22	45	M				Local	54	NED	11						11			NED
23	24	M		Y		Local	50.4	NED	17						17			NED
24	33	F				Local	54	PD	7	Local	1				7	Y	7	PD

Pt patient, *mo* month, *M* male, *F* female, *Y* yes, *blank* no, *NA* not applicable, *M+* spinal metastasis, *GTR* gross total tumor removal, *NAC* neoadjuvant chemotherapy, *CSI* craniospinal irradiation, *RT* radiation, *NED* no evidence of disease, *PR* partial response, *SD* stable disease, *PD* progression of disease, *PFS* progression-free survival, *LMM* intracranial leptomeningeal metastasis, *combined* both brain and spine progression, *RS* radiosurgery, *CMT* chemotherapy, *F/U* follow-up, *TTD* time to death

dimensional conformal RT (3DCRT), intensity-modulated RT (IMRT), and mixed 3DCRT/IMRT were used for most of the patients. In addition, the local field radiation was used more commonly in the later part of the study.

Before 2010, no imaging fusion system was used in the old treatment planning system. Target volumes were delineated with MRI fusion since 2010 with Eclipse version 8.9 (Palo Alto, CA, USA) rigid registration, which was later replaced with Eclipse version 13 (Palo Alto, CA, USA) rigid registration in 2017. The gross tumor volume (GTV) and clinical target volume (CTV) were modified mainly according to clinician preference. The local field RT target volume was residual tumor and tumor bed plus a 1–1.5-cm margin, with the exclusion of the anatomical boundaries of normal tissue. Wide-field RT target volumes were similar to the local field RT volumes, except that hyperintense T2 and peritumoral edema were also included in the GTV. The planning target volume (PTV) was a 0.5–1-cm uniform expansion of the CTV. Total doses of 50–60 Gy were prescribed, with daily doses of 1.8–2 Gy/fraction. The total radiation dose was dependent on the grading and location of the tumor.

All patients who underwent craniospinal irradiation (CSI) had evidence of spinal metastasis, except for one patient who only had evidence of intracranial subarachnoid seeding. The patient treatment details are given in Table 1. The evaluations for spinal metastasis were as follows: ten patients had MRI spine only, ten patients had both MRI spine and CSF cytology, and four patients were not evaluated for spinal metastasis.

Post-RT evaluation

All patients were assessed clinically and radiographically at routine follow-up intervals. MRI of the brain and spine was usually performed at intervals of 3–4 months during the first few years. Patients who did not visit hospital for follow-up were called via telephone at the data cutoff point to assess their final status. Tumor recurrence was defined as any new lesion or an increase in the size of a previous lesion on follow-up imaging. Response to RT was evaluated by a change in the maximal tumor diameter on the latest imaging study or the one that showed tumor progression according to RECIST criteria. Date of death was confirmed by the central government office.

Statistical analysis

Continuous variables are presented as median and range, and categorical variables are presented as frequency and percentage. The primary endpoint, the progression-free survival (PFS) rate, was defined as the time from completion of RT until tumor progression (detected by clinical or imaging study). Overall survival (OS) was defined as the time from completion of RT until the date of death or last contact with the patient. Survival probability was calculated using the Kaplan–Meier methods and compared using the log-rank test. Univariate analysis with the log-rank test was performed to identify potential factors affecting progression-free survival. These potential factors included gender, age less than 3 years at diagnosis and also at time of RT, tumor grade, location of tumor, spinal metastasis, extent of resection, neoadjuvant chemotherapy, RT technique, RT machine, field of RT, RT dose of 54 Gy or higher, RT dose of 59.4 Gy or higher, and RT treatment duration of less than 50 days. Factors associated with improved PFS were also analyzed for OS. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Result

On the data cutoff point of May 31, 2018, the median clinical follow-up time was 44.5 months (range, 1–146 months), and the median radiological follow-up

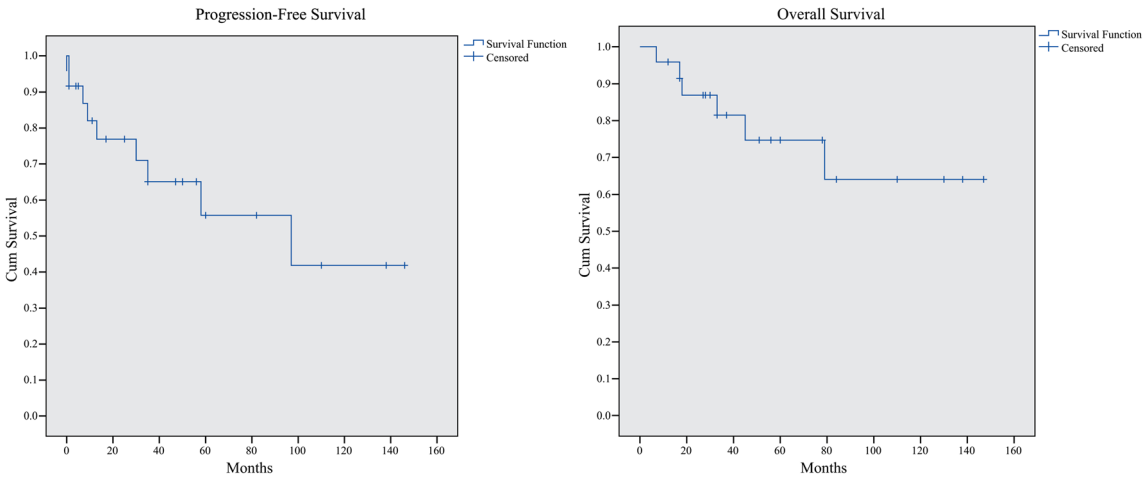

Fig. 1 Progression-free survival after RT (left) and overall survival (right) curves for all 24 patients

time was 42.5 months (range 1–137 months). Eight patients were lost to follow-up at our hospital, with five being alive without progression of symptoms, while the other three had died. The responses to radiation at 3–12 months were no evidence of disease in 14 (58%), partial response in 4 (17%), stable disease in 3 (12.5%), and tumor progression in 3 (12.5%). All patients with no evidence of disease had no residual tumor seen in the postoperative/preirradiative imaging.

Recurrence occurred in 9 of the total 24 patients (38%). Two of these recurrent patients (22%) had recurrences at multiple times. Details of recurrences and salvage treatments are shown in Table 2. The estimated 5-year PFS rate was 56%, with the median PFS being 97 months. There were six deaths:

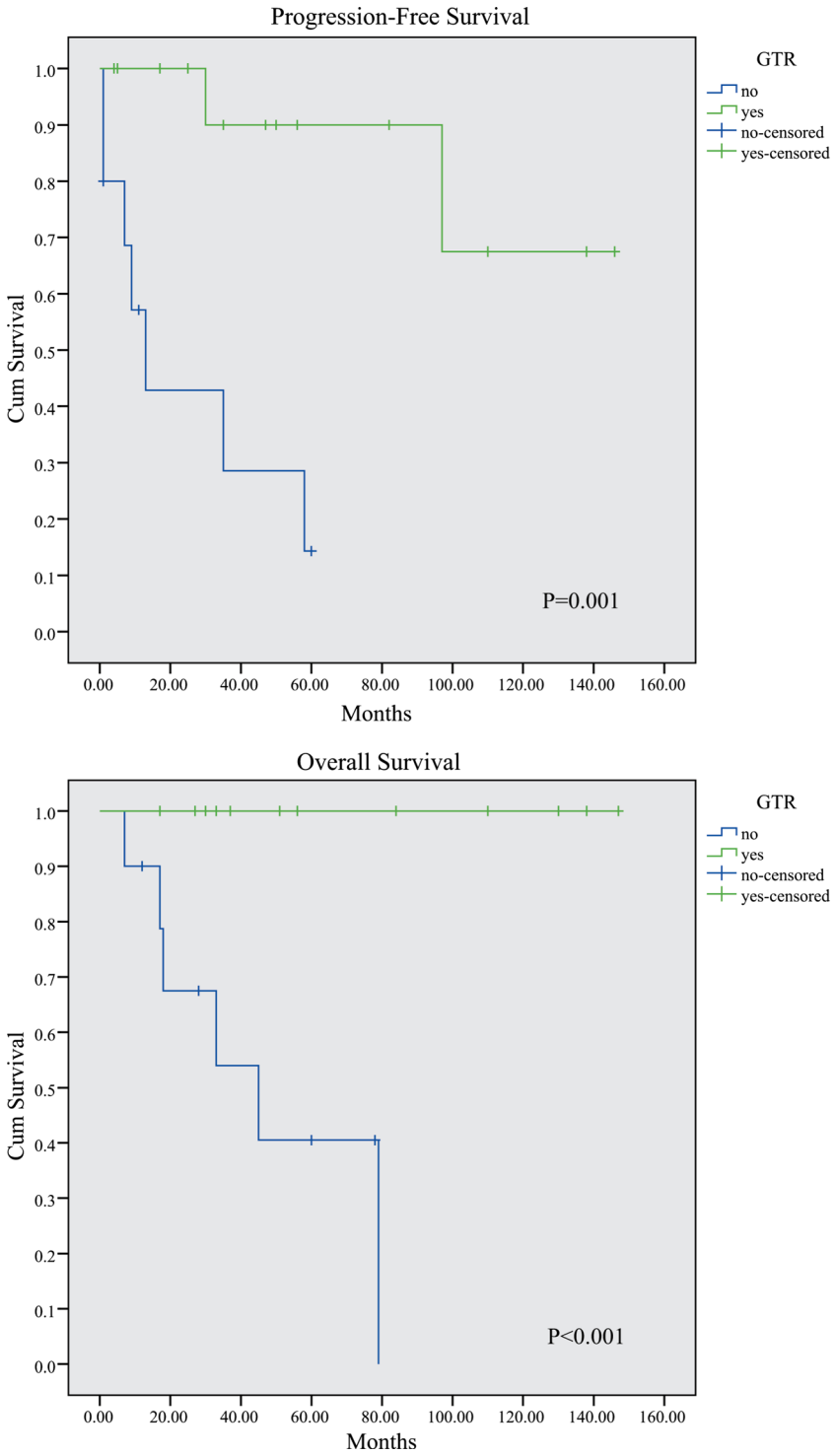

Fig. 2 Progression-free survival (above) and overall survival (below) curves for all 24 patients according to the extent of resection. GTR gross total tumor removal

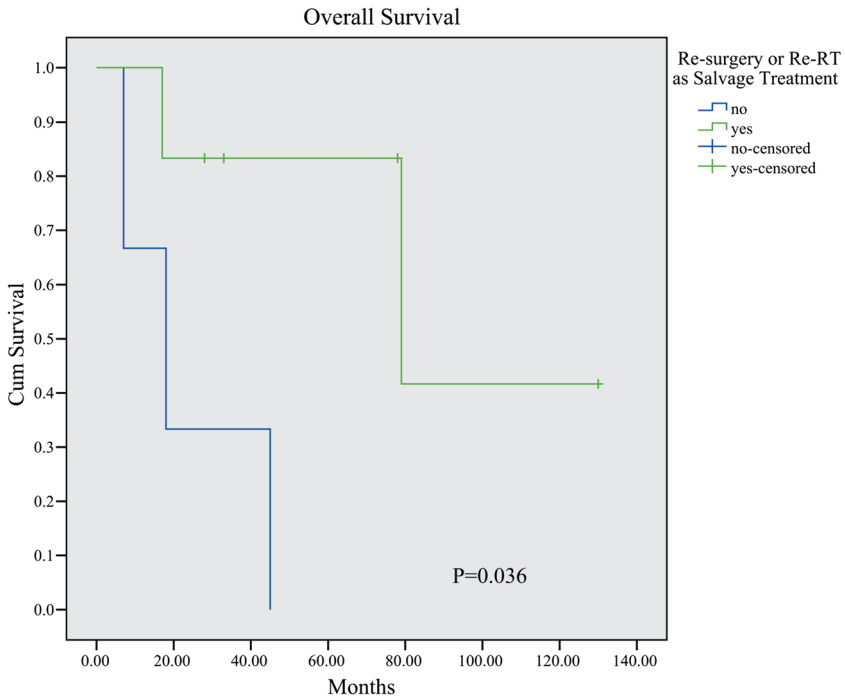

Fig. 3 Overall survival curve for the nine patients with recurrences, differentiated according to whether or not they underwent local salvage treatment

five with evidence of tumor progression and the other being of unknown cause. Eighteen patients (75%) were confirmed to be alive at the end of this study. The estimated 5-year OS rate was 75%. The median OS was not reached. The PFS and OS curves are shown in Fig. 1.

Univariate analysis showed that only the extent of resection was associated with improved PFS. The 5-year estimated PFS rates in gross total tumor removal (GTR) patients and non-GTR patients were 90% and 14%, respectively ($p = 0.001$). The extent of resection was also associated with improved 5-year estimated OS (100% vs 41%; $p < 0.001$). The PFS and OS curves for GTR and non-GTR patients are shown in Fig. 2.

Of the nine patients with recurrence, the six who underwent further surgery or further RT had better median overall survival than the three who did not, 79 months vs 18 months, respectively ($p = 0.036$; Fig. 3). Two patients developed intracranial leptomeningeal failure, one at 13 months and one at 9 months post-RT. The first patient received palliative oral etoposide as salvage treatment, while the other underwent sequential CSI and a maintenance combination of intravenous chemotherapy. The former died at 45 months of follow-up while the latter was still alive with disease progression at 28 months of follow-up.

No serious acute or late radiation complication was reported in the study patients.

Discussion

Childhood intracranial ependymoma patients who receive adjuvant radiation therapy have better PFS than those receiving surgery alone [3–5]. This benefit also applied to OS in one study [3]. However, there may be differences in ethnic or socioeconomic status between patients in the USA and Thailand. We therefore report on the outcomes of postoperative RT in both new and recurrent grade II and III intracranial ependymomas in children treated at Ramathibodi Hospital, Thailand.

The outcomes of the previous studies of pediatric intracranial ependymoma treated with radiation are summarized in Table 3, and our results are similar [6–14]. Our PFS rate was in the lower range described in the literature, but our OS rate was in the upper range; this could be due to aggressive salvage treatment. Two patients who had recurrences at multiple times (patient numbers 3 and 4 in Table 2) underwent multiple further surgeries, with or without radiosurgery, as salvage treatment. These further surgeries resulted in prolonged respective survival times of 33 and 44 months after the first recurrence detection. Even in a middle-income country, standard outcomes can be achieved with a multidisciplinary team for cancer management.

Although there is little available data, one study of pediatric ependymoma [13] reported that non-white patients were at a three-time higher risk of death compared with white patients. However, another study [13] found no impact of race on survival. Three previous studies found no significant difference in survival between male and female [6, 7, 11], although in contrast, Merchant et al. found worse PFS in male patients (HR 2.19; 95% CI 1.03–4.66; $p = 0.042$) [13]. Some studies have shown that younger patients (< 3 years) are significantly associated with worse local control and OS [13, 14], although

Table 3 Summary of outcome from other studies of intracranial ependymoma treated with radiotherapy

Author	Published	*n*	Med age at Dx (y)	Gr 3 (%)	IFT site (%)	M+ (%)	GTR (%)	Med dose (Gy)	Med FU (mo)	3-y DFS (%)	3-y OS (%)	5-y DFS (%)	5-y OS (%)	7-y DFS (%)	7-y OS (%)	Local failure (%)
Timmerman et al. [6]	2000	55	6.2	100	53	10	51	54	38	60	76					36
Schroeder et al. [7]	2007	22	6.6	64	55		77	54	39.8	68	87					27
Merchant et al. [8]	2004	88	2.85	15	65		85	54	38.2	75						15
Mansur et al. [9]	2004	60	10.7	33	80		23	50.4	150			58	71			
Paulino [10]	2002	28	12	14	100		61	54	127			60	81			14
Paulino et al. [11]	2001	49	14	22	67		43	54	115			69	69			40
Massimino et al. [12]	2009	63	NA	32	74	3	73	54	60			56	75			37
Merchant et al. [13]	2009	153	2.9	56	80		82	59.4	64					69	81	14
Shu et al. [14]	2007	49	5.5	22	63		61	55.8	110			41	66			53
Our study	–	24	3.7	58	58	17	58	54	44.5	65	82	56	75	56	64	29

n number of patients, *Gr* grade, *Dx* diagnosis, *y* year, *Med* median, *IFT* infratentorial, *M+* spinal metastasis present, *GTR* gross total tumor removal, *PFS* progression-free survival, *OS* overall survival, *mo* month

other studies did not identify such relationships between age and disease control after radiation [7–9, 11, 15]. However, conclusions with regard to patient age should be made with caution, because the cutoff ages for inclusion vary between the different studies and also the indications to adjuvant treatment such as radiation.

Previous studies have shown that anaplastic tumors are significantly associated with poorer PFS and OS compared with differentiated tumors [8, 11, 13, 14]. For example, Paulino et al. [11] found 5-year OS of 45.5% and 75.7%, respectively ($p = 0.035$). Merchant et al. [13] also reported HR for death of 3.98 unfavorable for anaplastic tumors (95% CI 1.21–7.44; $p = 0.018$). In contrast, others have not observed this association [7, 9]. The majority of relevant studies, including ours, suggest that patients who underwent total tumor removal had better survival than those who did not [6–8, 13, 14]. However, the studies of Mansur et al. [9] and Paulino et al. [11] did not find such a difference. Previous studies reported a correlation between total radiation dose and outcome. For example, Shu et al. [14] found that patients who received a prescribed dose of 54 Gy or higher had improved OS (HR 2.67; 95% CI 1.06–6.73) compared with those receiving less than 54 Gy. Taylor et al. [16] also reported a better outcome with RT doses of 45 to 50 Gy or higher compared with lower doses: 5-year OS of 51–69% vs 18–53%, respectively. In contrast, Schoreder et al. [7] and Mansur et al. [9] did not find such a correlation. Paulino et al. [17] showed that patients who had an RT treatment duration of less than 50 days had better 5-year OS than those with an RT treatment duration of 50 days or more (85.5% vs 45.5%; $p = 0.01$). However, the study of Schoreder et al. [7] did not find this association.

Our clinical follow-up time of 44.5 months is quite short compared with the recent study of Marinoff et al. [18]. They retrospectively reviewed 103 patients with median follow-up time of 11 years. They found that 10-year OS was 50% and 10-year PFS was 29%. They concluded that current treatment is not sufficient to provide long-term control of childhood ependymoma, and newer treatment for this disease is needed.

There were many recent studies focusing on treatment intensification such as adding chemotherapy or increasing RT dose to improve the outcome of this disease. The role of preirradiation chemotherapy in childhood intracranial ependymoma age 3 to 21 years was studied by Garvin et al. [19]. They found that the benefit of chemotherapy is restricted to patients with greater than 90% tumor resection. The second prospective AIEOP protocol for pediatric ependymoma by Massimino et al. [20] studied treatment intensification in 160 patients. The grade II tumor without residual

disease received standard focal RT while the grade III tumor without residual disease was given adjuvant chemotherapy after RT completion. Patients with residual tumor received chemotherapy, second-look surgery, and RT 59.4 Gy followed by an 8-Gy boost in two fractions on gross residual disease. The median follow-up time is 67 months. For the whole series, the 5-year PFS and OS were 65.4% and 81.1%, respectively. For patients with residual tumor, the 5-year PFS was 58.1% and the 5-year OS was 68.6%, which showed a trend of improvement in this group of patient with poor prognosis. The use of proton therapy can reduce the low and intermediate RT dose to the normal tissue and could lead to an increase in RT dose without severe toxicity. Indelicato et al. [21] reported the outcome of proton therapy in 179 children with ependymoma. The 3-year PFS and OS were 76% and 90%, respectively. They concluded that proton therapy had disease control rate comparable to photon series without unexpected toxicity.

Conclusion

Postoperative radiation is an effective treatment for pediatric intracranial ependymoma, benefiting from low complication rates. GTR is associated with better PFS and OS. Aggressive salvage local treatments for recurrent patients can result in good overall survival. Longer follow-up is needed in account for late relapse.

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Compliance with ethical standards This retrospective study was approved by our institutional ethics committee.

Conflict of interest The authors declare that they have no conflict of interest.

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