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The Effect of Initial Treatment Modality on Oncological Outcomes in Children with Ependymoma

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ABSTRACT

AIM: To evaluate the oncological outcomes and the prognostic factors for children with ependymoma who receive radiotherapy (RT) ± chemotherapy after surgery.

MATERIAL and METHODS: The medical records of 71 children with ependymoma who received RT between 2001 and 2022 were retrospectively evaluated. Survival outcomes and prognostic factors were analyzed using log-rank and cox-regression tests. SPSS v24.0 was utilized for statistical analyses.

RESULTS: Gross total resection (GTR) was achieved in 37 (52%) patients. Craniospinal fluid (CSF) seeding was observed in 8 (11%) patients at the time of diagnosis. The median RT dose was 54 Gy (42-60 Gy). The median time from surgery to the first RT was 2.4 months (1-109 months). The median follow-up time was 65.9 months (2.5-242.8 months), and 5-y overall survival, progression-free survival (PFS), and local recurrence-free survival (LRFS) were 74%, 39%, and 46%, respectively. Recurrence was observed in 41 (58%) patients. Among patients who initiated treatment with chemotherapy, 5-y PFS and LRFS were higher in patients who received RT at the time of diagnosis than those who received RT at the progression (23% vs. 0%, $p<0.001$ and 39% vs 0%, $p<0.001$). In multivariate analysis, increased time from surgery to radiotherapy was found to be a poor prognostic factor for PFS.

CONCLUSION: Young age, less than GTR, large residual tumor volume, initiation of treatment with chemotherapy after surgery, and increased time from surgery to radiotherapy may deteriorate survival. RT should not be delayed until progression, even in young patients receiving chemotherapy.

KEYWORDS: Ependymoma, Survival, Pediatric, Radiotherapy

ABBREVIATIONS: CSF: Craniospinal fluid, **CSI:** Craniospinal irradiation, **CTV:** Clinical target volume, **EFS:** Event-free survival, **GTV:** Gross tumor volume, **GTR:** Gross-total resection, **IMRT:** Intensity modulated radiotherapy, **LRFS:** Locoregional recurrence-free survival, **OS:** Overall survival, **PFS:** Progression-free survival, **PTV:** Planning target volume, **RT:** Radiotherapy, **STR:** Subtotal resection

INTRODUCTION

Ependymomas can occur at any age, but it has a peak incidence in early childhood (8). It is the third most common malignant brain tumor in children accounting for 6-12% of brain tumors (6). Pediatric ependymomas are mostly located in the posterior fossa, followed by supratentorial sites (8). Gross total resection (GTR) is the strongest predictor of outcome, however, the resectability of the tumor is highly dependent on the tumor site (22). Higher rates of GTR for supra-

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tentorial ependymomas may explain the better prognosis than the tumors located other than supratentorial sites (25). The cornerstone of treatment is adjuvant radiotherapy (RT) after definitive surgery to increase local control and survival (8,16). Chemotherapy has a limited role in the treatment of childhood ependymoma. Although it has been used as a neoadjuvant therapy to maintain second-look surgery for incompletely resected tumors or to postpone RT due to its possible long-term sequela in infants, its efficacy has not been proven so far (14,23,24). Furthermore, it was shown that delaying RT in very young children leads to increased recurrence rates and poorer survival (15). However, delaying RT is currently debated upon very few studies showing favorable results with prolonged adjuvant chemotherapy (4,21). In light of these data, we conducted this retrospective study to investigate the survival rates, the prognostic factors, and the effects of RT timing on oncological outcomes for patients receiving postoperative RT.

MATERIAL and METHODS

Patient and Treatment Characteristics

The medical records of 71 patients who were younger than 18 years and treated with radiotherapy for the diagnosis of ependymoma between 2001 and 2022 were retrospectively evaluated. All patients had a magnetic resonance imaging of brain and spine, a cerebrospinal fluid (CSF) analysis at the time of diagnosis for staging, and a brain magnetic resonance imaging after surgery to evaluate whether a residual tumor remained. Surgery, including gross or subtotal resection (STR) was performed in all patients. Patients who were younger than three years old initiated the treatment with chemotherapy after surgery, and RT was delayed until three years old or until tumor progression. Patients who were older than three years old initiated the treatment with RT or chemotherapy after surgery. Patients with a previous history of RT to brain or spinal region or who received CT previously were excluded from this study.

All patients received GTR or STR. After surgery, 2D, 3D conformal, or intensity-modulated RT (IMRT) was administered in all patients. Only the patients who were unable to cooperate during RT received RT under anesthesia. All patients without CSF seeding received RT at the local field, and craniospinal irradiation was performed for patients who had microscopic or macroscopic seeding. Additionally, a boost dose to metastatic fields was performed in patients who had localized macroscopic seeding in magnetic resonance imaging. Gross tumor volume (GTV) included the tumor bed and the residual tumor for patients who received local RT. Clinical target volume (CTV) was defined as a 1 cm extension from GTV, and planning target volume (PTV) was generated by adding 0.3 cm to 0.5 cm to CTV. CTV involved prophylactic irradiation of the entire craniospinal axis, with an additional focal boost to tumor sites, and PTV was generated with a 0.3 to 0.5 cm margin to CTV in patients who received craniospinal irradiation (CSI). Local RT was administered up to 60 Gy, and CSI was performed at a dose of 36 Gy, followed by a localized boost to 54-60 Gy.

This study was conducted in accordance with the declaration of Helsinki and informed consent was obtained from each patient. Ethical approval for this study was provided by the institutional review board (GO 22/637).

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM, Armonk, NY; USA). Based on the different initial treatment modalities, the primary endpoints were recurrence rate, overall survival (OS), progression-free survival (PFS), and local recurrence-free survival (LRFS). The secondary endpoints were prognostic factors for recurrence, OS, PFS, and LRFS. Local recurrence was defined as recurrences in the RT field or progressions from the primary tumor location. Distant brain recurrence and spinal recurrence were defined as recurrences out of the RT field or outside the primary tumor location within the brain and in the spinal region, respectively. All time-related parameters were calculated from the last date of the treatment to the last follow-up, recurrence, or death, whichever came first. The associations between clinical parameters and local recurrence rates were analyzed with a chi-square test. Survival estimates were calculated using Kaplan-Meier analyses, and group survival comparisons were performed with a log-rank test. Possible factors with a p-value of <0.10 in univariate analyses were further entered into the cox-regression analysis, with backward selection, to determine independent predictors of survival (17). A p-value of <0.05 was considered statistically significant.

RESULTS

Patient and Tumor Characteristics

The median age was four years (range, 1-18 years), and 19 (27%) patients were younger than three years. Forty-six (65%) patients were male. Forty-seven (66%) patients had infratentorial and 24 (34%) patients had supratentorial tumors. The infratentorial tumors arise most frequently in the fourth ventricle (%74), followed by cerebellum (22%), vermis (2%), and extra-axial location (2%). The median residual tumor volume was 15 mm^3 (range, 1-66 mm^3). Histopathologic evaluation demonstrated that 29 (48%) patients had grade 2, 31 (52%) patients had grade 3 ependymoma, and the grade was unknown in 11 patients. ZFTA fusion status was investigated in only four patients, and three of four had ZFTA fusion-positive tumors. The patient characteristics are summarized in Table I.

Treatment Outcomes

GTR and STR were achieved in 37 (52%) and 34 (48%) patients, respectively. Neither age nor tumor location affected the rates of GTR (42% and 56%, p=0.308 for patients <three years and three years of age; 46% and 55%, p=0.449 for supra- and infratentorial lesions, respectively). When we performed subgroup analyses among patients with infratentorial located tumors, we observed that rates of GTR were similar between patients with intra- and extraventricular lesions (56% vs 50%, p=0.725). While 62 (87%) patients received RT to the primary tumor at the time of diagnosis, nine (13%) patients received RT to the primary tumor when progression was detected.

Table I: Comparison of Patient Characteristics According to Age

Clinical Parameters	Categorization According to Age		p-value
	≥ 3 years n=52 (%)	< 3 years n=19 (%)	
Surgery			
Gross total resection	29 (56)	8 (42)	0.308
Subtotal resection	23 (44)	11 (58)	
Residual tumor volume (mm^3)			
≥ 15	4 (7)	4 (21)	0.662
< 15	9 (17)	5 (26)	
Unknown	10 (20)	2 (11)	
Cerebrospinal fluid seeding			
Present	6 (12)	2 (11)	1.000
Absent	46 (88)	17 (89)	
Tumor location			
Supratentorial	20 (39)	4 (21)	0.170
Infratentorial	32 (61)	15 (79)	
Initial treatment modality after surgery			
Radiotherapy	34 (65)	3 (16)	**<0.001**
Chemotherapy	6 (12)	12 (63)	
Unknown	12 (23)	4 (21)	
Timing of radiotherapy			
At the time of diagnosis	48 (92)	14 (74)	0.051
At the time of progression	4 (8)	5 (26)	
Time from surgery to radiotherapy (months)			
> 2.4	17 (33)	15 (79)	**0.001**
≤ 2.4	32 (61)	4 (21)	
Unknown	3 (6)	0	
Time from surgery to chemotherapy (months)			
> 1	13 (25)	8 (42)	0.747
≤ 1	14 (27)	7 (37)	
Unknown	25 (48)	4 (21)	
Radiotherapy Field			
Local	39 (75)	13 (68)	0.431
Craniospinal Irradiation	9 (17)	1 (6)	
No radiotherapy at diagnosis	4 (8)	5 (26)	
Radiotherapy Dose (Gy)			
≥ 54	34 (65)	10 (53)	1.000
< 54	14 (27)	4 (21)	
No radiotherapy at diagnosis	4 (8)	5 (26)	

CSI and local RT were performed on 13 (19%) and 58 (81%) patients, respectively. Twenty-six (37%), 16 (22%), and 29 (41%) patients received RT with 2D, 3D, and IMRT techniques, respectively.

The median RT dose was 54 Gy (range 42-60 Gy). In all cohorts, the median time from surgery to RT and chemotherapy was 2.4 months (range, 1-109 months) and one month (range, 0.3-21.9 months), respectively. Treatment was initiated with RT and chemotherapy in 37 (52%) and 18 (25%) patients, respectively. The sequence of the treatment was unknown in 16 (23%) patients. The median time from surgery to RT was 1.8 months (range, 1-19 months) in patients who initiated treatment with RT after surgery. Eighteen (33%) patients received chemotherapy before RT, and the median number of chemotherapy cycles was 5 (range, 3-9) in this group of patients. Forty-eight (79%) patients received adjuvant chemotherapy after RT, and the median adjuvant chemotherapy cycle was 6 (range, 3-10). The most common chemotherapy regimen was

cisplatin-etoposide (79%), followed by carboplatin-etoposide (15%), cisplatin-vincristine (2%), cisplatin-etoposide-vincristine (2%), and carboplatin-etoposide-vincristine (2%).

The median follow-up was 65.9 months (range, 2.5-242.8 months). Local recurrence, distant brain recurrence, and spinal recurrence were observed in 37 (52%), 2 (3%), and 3 (4%), respectively. Four (22%) of 18 patients who initiated treatment with chemotherapy first received RT when residual disease progressed, and 14 patients received RT before progression.

At the time of diagnosis, eight (11%) patients had CSF seeding. Primary tumor location was infratentorial in seven patients who had CSF seeding at the diagnosis. In this group, GTR and STR at the primary site were achieved in two and six patients, respectively. Seven patients who had CSF seeding received craniospinal RT at the time of diagnosis. A four-month-old patient received chemotherapy first, and RT at a dose of 24 Gy was performed on the craniospinal field for CSF seeding when progression was detected. This patient died due to progressive disease. Six of eight patients who were treated with CSI at the time of diagnosis had a recurrence, most commonly arising from infratentorial (66%) followed by supratentorial (17%) and spinal (17%) area.

Five- and ten-y OS, PFS, and LRFS were 74% and 65%, 39% and 31%, 46% and 40%, respectively. Five-year OS was lower in patients with recurrence compared to those without recurrence (65% vs 92%, p<0.001). While subgroup analysis was performed for those who initiated treatment with chemotherapy, five-y OS was similar between patients who received RT at the time of diagnosis and at the time of progression (59% vs. 75%, p=0.844), but 5-y PFS and LRFS were higher in patients who received RT at the time of diagnosis than those received RT at the time of progression (23% vs 0%, p<0.001 and 39% vs 0%, p<0.001, respectively) (Figure 1). Five-y OS, PFS, and LRFS were similar between patients with and without craniospinal seeding at the time of diagnosis (83% vs. 71%, p=0.834; 50% vs 38%, p=0.670; 50% vs 45%, p=0.415).

Univariate analysis revealed that residual tumor volume and type of surgery were a significant factor for OS and local recurrence, respectively. The type of surgery was a marginally

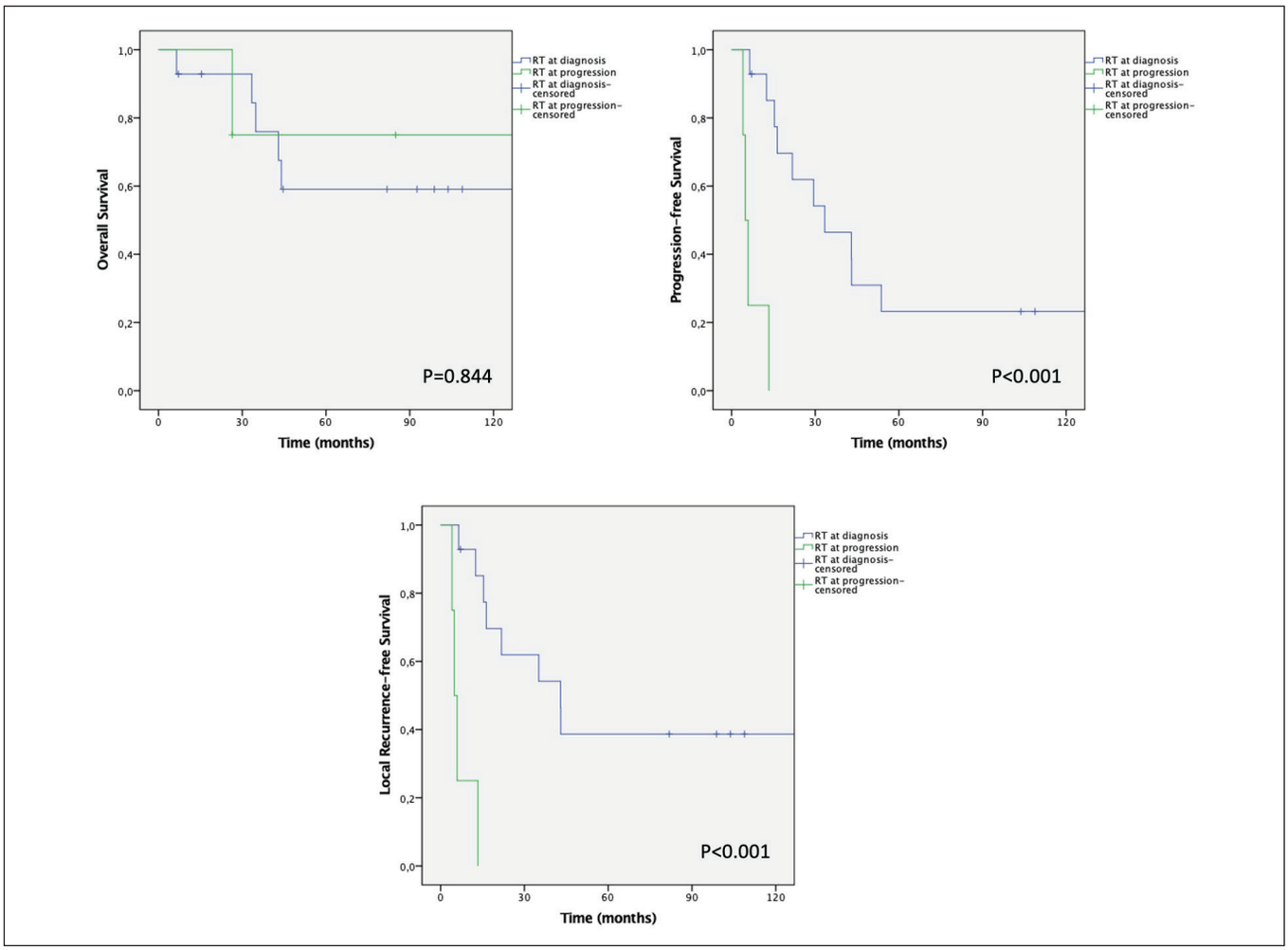

Figure 1: Kaplan-Meier curves for overall survival, progression-free survival, and locoregional recurrence-free survival in patients who initiated treatment with chemotherapy.

significant factor for OS. Age and type of surgery were also significant factors for PFS. Initial treatment modality after surgery and time from surgery to radiotherapy were marginally significant factors for PFS (Table II). Since residual tumor volume and type of surgery was the only significant factor for OS and local recurrence, respectively, no further multivariate analyses were performed. Multivariate analysis showed that time from surgery to radiotherapy was an independent factor for PFS (Table III).

Table II: Univariate Analysis of Prognostic Factors for Local Recurrence, 5-Year Overall Survival (OS) and Progression-Free Survival (PFS)

	Local Recurrence Rate (%)	p-value	5-y OS (%)	p-value	5-y PFS (%)	p-value
Age (years)						
≥ 3	52	0.958	76	0.253	51	**0.021**
< 3	53		64		12	
Surgery						
Gross total resection	35	**a**	83	0.105	50	**0,017**
Subtotal resection	71		65		31	
Residual tumor volume (mm^3)						
≥ 15	75	1.000	73	**0.046**	25	0.670
< 15	64		91		32	
Cerebrospinal fluid seeding						
Present	75	0.264	83	0.834	50	0.670
Absent	49		71		38	
Tumor location						
Supratentorial	50	0.799	70	0.634	33	0.329
Infratentorial	53		76		45	
Initial treatment modality after surgery						
Radiotherapy	54	0.778	82	0.410	52	0.066
Chemotherapy	50		61		18	
Time from surgery to radiotherapy (months)						
> 2.4	53	0.627	69	0.555	29	0.085
≤ 2.4	47		74		48	
Time from surgery to chemotherapy (months)						
> 1	57	0.537	71	0.193	22	0.146
≤ 1	48		72		41	
Radiotherapy Field						
Local	40	0.163	70	0.734	44	0.704
Craniospinal Irradiation	70		88		56	
Radiotherapy Dose (Gy)						
≥ 54	46	0.942	67	0.324	39	0.493
< 54	44		88		60	

Table III: Multivariate Analysis of Independent Prognostic Factors for 5-Year Progression-Free Survival (PFS)

Event	HR (95% CI)	p-value
5-y Progression-Free Survival		
Time from surgery to radiotherapy (Reference: ≤2.4 months) >2.4 months	3.277 (1.040 to 10.329)	0.043

DISCUSSION

The OS rates in this study were compatible with the literature, while PFS rates were lower than most of the recent studies (10-12). Some of these studies have an exclusion criterion of being three years old, which has been reported as a poor prognostic factor for ependymoma. In contrast, 19 patients were younger than three years old in the current study (12). Additionally, the lower PFS rates might be attributed to 18 (25%) patients starting treatment with chemotherapy, which delayed RT for this group. However, the PFS rates in the current study were similar to those in the study by Garvin et al., which investigated the outcomes of patients receiving preirradiation chemotherapy (3).

The current study also showed that in a subgroup of patients who received chemotherapy first, the five-year PFS and LRFS were higher in patients receiving RT at the time of diagnosis compared to those receiving RT at progression (23% vs. 10% and 39% vs 0%). Although the current treatment strategy for childhood ependymoma is maximal surgical resection followed by adjuvant RT, delaying RT is still controversial due to its severe late adverse effects in young children (4,21). Grill et al. tried to omit or delay RT to the time of relapse in the presence of chemotherapy and concluded that deferring RT at the time of relapse did not compromise OS. However, four-y PFS and five-y OS rates were 22% and 52%, respectively, in that study, which is lower than the current study (4). Timmermann et al. also investigated delaying or omitting RT in young children in the presence of chemotherapy and found that three-y OS and PFS rates were 55.9% and 27.3%, respectively (23). Therefore, the authors concluded that delaying RT compromised survival, even in cases undergoing intensive chemotherapy (23). Merchant et al. also demonstrated that patients who received preirradiation chemotherapy had poorer three-y PFS rates, which was adjusted for age (49±12% vs. 84±10%, p=0.056) than those who did not (15). ACNS0121 trial also recently demonstrated that event-free survival (EFS) for patients with ependymoma younger than three years of age who received immediate postoperative RT and older than three years of age was similar and concluded that RT should remain the mainstay of ependymoma treatment (14).

On the contrary, Strother et al. investigated the benefit of prolonged dose-intensive chemotherapy for infants with malignant brain tumors and demonstrated that prolonged intensive chemotherapy resulted in increased EFS for patients with ependymoma (21). UKCCSG/SIOP prospective study also recommended delaying RT until progression in young children without compromising survival (5). A recent study by Shah et al. did not observe a difference between patients who initiated RT ≤five weeks, five-eight weeks, and > eight weeks after surgery (20). However, these findings can not be interpreted in favor of delaying RT since the effect of RT initiation, whether at the time of diagnosis or progression of oncological outcomes were not evaluated in this study (20). Currently, the efficacy of chemotherapy is still not proven, but the value of chemotherapy in ependymoma treatment is being evaluated in the ongoing SIOP Ependymoma II trial (9). The current study also demonstrated that increased time (>2.4 months) from surgery to radiotherapy was an independent poor prognostic factor for PFS, and five-y PFS and LRFS were higher in patients who received RT at the time of diagnosis than those received RT at the time of progression among patients who initiated treatment with chemotherapy. In light of these data, we recommend not delaying RT to the time of progression even in young children because of compromised survival rates. Clinicians should consider administering RT as soon as possible even if the patient received chemotherapy first due to young age.

Moreover, the present study explored prognostic factors for childhood ependymoma. It revealed that young age, subtotal resection (STR), large residual tumor volume, receiving chemotherapy as the initial treatment modality after surgery, and an increased time from surgery to radiotherapy were poor prognostic factors for survival in ependymoma patients. Unlike most other primary brain tumors, prognostic factors that affect oncological outcomes in childhood ependymoma have not been well established. Most series showed a predictive value of GTR on survival; however, the importance of other prognostic factors such as age, tumor grade, tumor location, leptospinal dissemination, and initial treatment modality remains controversial (1,4,7,13,15,23). Although the current study demonstrated the prognostic impact of GTR on survival, rates of GTR were only 52% in this study. The low rates of gross total resection (GTR) could likely be attributed to the significant proportion of patients referred to our center for radiotherapy after surgery elsewhere. Unfortunately, we lack details regarding the surgical procedures for this subgroup of patients. Furthermore, cranial nerves and brain stem vasculature adjacent to the tumor might have limited the extent of the surgery, especially posterior fossa tumors, which constitute almost 70% of all tumors in this study (19).

Young age was identified as a poor prognostic factor for childhood ependymoma in most studies in the literature, including the current study. However, findings from a SEER database analysis and a French Society of Pediatric Oncology group trial did not show a significant effect of age on survival (1,4). It's noteworthy that the cutoff values for these studies were 2 and 5 years old, which were not commonly utilized in the literature. Additionally, tumor grade was shown to be a prognostic factor for survival in a few studies (1,10,15). However, McLendon et al. demonstrated that perinecrotic CA IX localization and MIB-1 labeling index were predictive biomarkers for survival, unlike tumor grade (13). Currently, molecular prognostic markers have been increasingly studied for risk stratification in childhood ependymoma (26). Studies showed that molecular classification better demonstrates clinical heterogeneity between subclasses of ependymoma than the histopathological grading system (2). Furthermore, gene expression signatures have shown the highest prognostic value among other studied molecular criteria (26). Ritzman et al. showed an increased relapse rate in EPN_PFA and EPN_RELA groups and in the presence of 1q gain compared to other groups (18). Thus, future studies investigating the optimal treatment for ependymoma should rely on molecular differences among ependymoma subtypes.

The current study has some limitations due to its retrospective nature. The most important limitation of this study is the lack of molecular grouping since the molecular subgroups were not defined in the early 2000s when the treatments began in this study. Therefore, molecular evaluation can be performed in only a small number of patients. Another limitation of this study is the lack of information regarding the initial treatment after surgery in 22.5% of our cohort. This is due to the retrospective nature of data collection and the fact that a significant proportion of patients were referred to our center for radiotherapy. Additionally, it is uncertain whether these patients received chemotherapy before referral. To overcome this limitation, we performed a separate analysis among patients who were known to initiate the treatment with chemotherapy and compared RT at diagnosis with RT at progression among these patients. We also could not access the toxicity information of these patients due to the retrospective nature of this study. However, this study is one of the largest series in the literature investigating the effect of treatment modality at initiation and time from surgery to radiotherapy on oncological outcomes. In conclusion, this study highlights several factors associated with poorer survival outcomes, including young age, less than gross total resection (GTR), large residual tumor volume, initiation of treatment with chemotherapy after surgery, and increased time from surgery to radiotherapy. It underscores the importance of not delaying radiotherapy until disease progression, even in young patients undergoing chemotherapy.

Declarations

Funding: No funding was received for this work.

Availability of data and materials: The data set used for the present study is available from the corresponding author upon reasonable request.

Disclosure: The authors report no conflicts of interest.

Ethics Approval: Our institutional ethics committee approved this study.

Patient Consent Statement: All patients consented to their anonymized data being used for research and educational purposes.

AUTHORSHIP CONTRIBUTION

Study conception and design: GY, CSBE
Data collection: PB
Analysis and interpretation of results: CSBE, PB
Draft manuscript preparation: CSBE, PB
Critical revision of the article: GY, GBA, FS, BB, TK, FZ
Other (study supervision, fundings, materials, etc...): GY
All authors (CSBE, PB, GY, GBA, FS, BB, TK, FZ) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Amirian ES, Armstrong TS, Aldape KD, Gilbert MR, Scheurer ME: Predictors of survival among pediatric and adult ependymoma cases: A study using Surveillance, Epidemiology, and End Results data from 1973 to 2007. Neuroepidemiology 39:116-124, 2012. https://doi.org/10.1159/000339320
2. Ellison DW, Kocak M, Figarella-Branger D, Felice G, Catherine G, Pietsch T, Frappaz D, Massimino M, Grill J, Boyett JM, Grundy RG: Histopathological grading of pediatric ependymoma: Reproducibility and clinical relevance in European trial cohorts. J Negat Results Biomed 10:7, 2011. https://doi.org/10.1186/1477-5751-10-7
3. Garvin JH Jr, Selch MT, Holmes E, Berger MS, Finlay JL, Flannery A, Goldwein JW, Packer RJ, Rorke-Adams LB, Shiminski-Maher T, Sposto R, Stanley P, Tannous R, Pollack IF; Children's Oncology Group: Phase II study of pre-irradiation chemotherapy for childhood intracranial ependymoma. Children's Cancer Group protocol 9942: A report from the Children's Oncology Group. Pediatr Blood Cancer 59:1183-1189, 2012. https://doi.org/10.1002/pbc.24274
4. Grill J, Le Deley MC, Gambarelli D, Raquin MA, Couanet D, Pierre-Kahn A, Habrand JL, Doz F, Frappaz D, Gentet JC, Edan C, Chastagner P, Kalifa C; French Society of Pediatric Oncology: Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: A multicenter trial of the French Society of Pediatric Oncology. J Clin Oncol 19:1288-1296, 2001. https://doi.org/10.1200/JCO.2001.19.5.1288
5. Grundy RG, Wilne SA, Weston CL, Robinson K, Lashford LS, Ironside J, Cox T, Chong WK, Campbell RHA, Bailey CC, Gattamaneni R, Picton S, Thorpe N, Mallucci C, English MW, Punt JAG, Walker DA, Ellison DW, Machin D; Children's Cancer and Leukaemia Group (formerly UKCCSG) Brain Tumour Committee: Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: The UKCCSG/SIOP prospective study. Lancet Oncol 8:696-705, 2007. https://doi.org/10.1016/S1470-2045(07)70208-5
6. Hammad M, Hosny M, Khalil EM, Alfaar AS, Fawzy M: Pediatric ependymoma: A single-center experience from a developing country. Indian J Cancer 58:378-386, 2021. https://doi.org/10.4103/ijc.IJC_373_19
7. Jaing TH, Wang HS, Tsay PK, Tseng CK, Jung SM, Lin KL, Lui TN: Multivariate analysis of clinical prognostic factors in children with intracranial ependymomas. J Neurooncol 68: 255-261, 2004. https://doi.org/10.1023/B:NEON.0000033383.84900.c1
8. Junger ST, Timmermann B, Pietsch T: Pediatric ependymoma: An overview of a complex disease. Childs Nerv Syst 37:2451-2463, 2021. https://doi.org/10.1007/s00381-021-05207-7
9. Leblond P, Massimino M, English M, Ritzmann TA, Gandola L, Calaminus G, Thomas S, Pérol D, Gautier J, Grundy RG, Frappaz D: Toward improved diagnosis accuracy and treatment of children, adolescents, and young adults with ependymoma: The international SIOP ependymoma II protocol. Front Neurol 13:887544, 2022. https://doi.org/10.3389/fneur.2022.887544
10. Marinoff AE, Ma C, Guo D, Snuderl M, Wright KD, Manley PE, Al-Sayegh H, Sinai CE, Ullrich NJ, Marcus K, Haas-Kogan D, Goumnerova L, London WB, Kieran MW, Chi SN, Fangusaro J, Bandopadhayay P: Rethinking childhood ependymoma: A retrospective, multi-center analysis reveals poor long-term overall survival. J Neurooncol 135:201-211, 2017. https://doi.org/10.1007/s11060-017-2568-8

11. Massimino M, Barretta F, Modena P, Witt H, Minasi S, Pfister SM, Pajtler KW, Antonelli M, Gandola L, Luisa Garrè M, Bertin D, Mastronuzzi A, Mascarin M, Quaglietta L, Viscardi E, Sardi I, Ruggiero A, Pollo B, Buccoliero A, Luna Boschetti L, Schiavello E, Chiapparini L, Erbetta A, Morra I, Gessi M, Donofrio V, Patriarca C, Giangaspero F, Johann P, Buttarelli FR: Second series by the Italian Association of Pediatric Hematology and Oncology of children and adolescents with intracranial ependymoma: An integrated molecular and clinical characterization with a long-term follow-up. Neuro Oncol 23:848-857, 2021. https://doi.org/10.1093/neuonc/noaa257
12. Massimino M, Miceli R, Giangaspero F, Boschetti L, Modena P, Antonelli M, Ferroli P, Bertin D, Pecori E, Valentini L, Biassoni V, Garrè ML, Schiavello E, Sardi I, Cama A, Viscardi E, Scarzello G, Scoccianti S, Mascarin M, Quaglietta L, Cinalli G, Diletto B, Genitori L, Peretta P, Mussano A, Buccoliero A, Calareso G, Barra S, Mastronuzzi A, Giussani C, Marras CE, Balter R, Bertolini P, Giombelli E, La Spina M, Buttarelli FR, Pollo B, Gandola L: Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma. Neuro Oncol 18:1451-146, 2016. https://doi.org/10.1093/neuonc/now108
13. McLendon RE, Lipp E, Satterfield D, Ehinger M, Austin A, Fleming D, Perkinson K, Lefaivre M, Zagzag D, Wiener B, Gururangan S, Fuchs H, Friedman HS, Herndon 2nd JE, Healy P: Prognostic marker analysis in pediatric intracranial ependymomas. J Neurooncol 122:255-261, 2015. https://doi.org/10.1007/s11060-014-1711-z
14. Merchant TE, Bendel AE, Sabin ND, Burger PC, Shaw DW, Chang E, Wu S, Zhou T, Eisenstat DD, Foreman NK, Fuller CE, Anderson ET, Hukin J, Lau CC, Pollack IF, Laningham FH, Lustig RH, Armstrong FD, Handler MH, Williams-Hughes C, Kessel S, Kocak M, Ellison DW, Ramaswamy V: Conformal radiation therapy for pediatric ependymoma, chemotherapy for incompletely resected ependymoma, and observation for completely resected, supratentorial ependymoma. J Clin Oncol 37:974-983, 2019. https://doi.org/10.1200/JCO.18.01765
15. Merchant TE, Jenkins JJ, Burger PC, Sanford RA, Sherwood SH, Jones-Wallace D, Heideman RL, Thompson SJ, Helton KJ, Kun LE: Influence of tumor grade on time to progression after irradiation for localized ependymoma in children. Int J Radiat Oncol Biol Phys 53:52-57, 2002. https://doi.org/10.1016/S0360-3016(01)02801-2
16. Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA: Conformal radiotherapy after surgery for paediatric ependymoma: A prospective study. Lancet Oncol 10:258-266, 2009. https://doi.org/10.1016/S1470-2045(08)70342-5
17. Mickey RM, Greenland S: The impact of confounder selection criteria on effect estimation. Am J Epidemiol 129:125-137, 1989. https://doi.org/10.1093/oxfordjournals.aje.a115101
18. Ritzmann TA, Rogers HA, Paine SML, Storer LCD, Jacques TS, Chapman RJ, Ellison D, Donson AM, Foreman NK, Grundy RG: A retrospective analysis of recurrent pediatric ependymoma reveals extremely poor survival and ineffectiveness of current treatments across central nervous system locations and molecular subgroups. Pediatr Blood Cancer 67:e28426, 2020. https://doi.org/10.1002/pbc.28426
19. Ruda R, Bruno F, Pellerino A, Soffietti R: Ependymoma: Evaluation and management updates. Curr Oncol Rep 24: 985-993, 2022. https://doi.org/10.1007/s11912-022-01260-w
20. Shah S, Gates K, Mallory C, Rubens M, Maher OM, Niazi TN, Khatib Z, Kotecha R, Mehta MP, Hall MD: Effect of postoperative radiation therapy timing on survival in pediatric and young adult ependymoma. Adv Radiat Oncol 6:100691, 2021. https://doi.org/10.1016/j.adro.2021.100691
21. Strother DR, Lafay-Cousin L, Boyett JM, Burger P, Aronin P, Constine L, Duffner P, Kocak M, Kun LE, Horowitz ME, Gajjar A: Benefit from prolonged dose-intensive chemotherapy for infants with malignant brain tumors is restricted to patients with ependymoma: A report of the Pediatric Oncology Group randomized controlled trial 9233/34. Neuro Oncol 16:457-465, 2014. https://doi.org/10.1093/neuonc/not163
22. Tamburrini G, D'Ercole M, Pettorini BL, Caldarelli M, Massimi L, Di Rocco C: Survival following treatment for intracranial ependymoma: A review. Childs Nerv Syst 25:1303-1312, 2009. https://doi.org/10.1007/s00381-009-0874-y
23. Timmermann B, Kortmann RD, Kuhl J, Rutkowski S, Dieckmann K, Meisner C, Bamberg M: Role of radiotherapy in anaplastic ependymoma in children under age of 3 years: results of the prospective German brain tumor trials HIT-SKK 87 and 92. Radiother Oncol 77:278-285, 2005. https://doi.org/10.1016/j.radonc.2005.10.016
24. Upadhyaya SA, Robinson GW, Onar-Thomas A, Orr BA, Billups CA, Bowers DC, Bendel AE, Hassall T, Crawford JR, Partap S, Fisher PG, Tatevossian RG, Seah T, Qaddoumi IA, Vinitsky A, Armstrong GT, Sabin ND, Tinkle CL, Klimo P, Indelicato DJ, Boop FA, Merchant TE, Ellison DW, Gajjar A: Molecular grouping and outcomes of young children with newly diagnosed ependymoma treated on the multi-institutional SJYC07 trial. Neuro Oncol 21:1319-1330, 2019. https://doi.org/10.1093/neuonc/noz069
25. Vaidya K, Smee R, Williams JR: Prognostic factors and treatment options for paediatric ependymomas. J Clin Neurosci 19:1228-1235, 2012. https://doi.org/10.1016/j.jocn.2012.02.006
26. Zaytseva M, Papusha L, Novichkova G, Druy A: Molecular stratification of childhood ependymomas as a basis for personalized diagnostics and treatment. Cancers (Basel) 130: 4954, 2021. https://doi.org/10.3390/cancers13194954