original article

Survival after therapy for pediatric ependymoma in a tertiary care center in Saudi Arabia

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BACKGROUND: There is limited data from Saudi Arabia on the demographic characteristics, outcomes and effectiveness of different treatment modalities in children with intracranial ependymoma.

OBJECTIVE: Study the characteristics of pediatric ependymoma and outcomes of treatment modalities in Saudi Arabia.

DESIGN: Retrospective.

SETTING: Tertiary care center.

PATIENTS AND METHODS: Children with intracranial ependymoma who were younger than 14 years of age and treated between 2006 and 2015 were included in the study. Patients with prior radiation, chemotherapy, or surgical resection at other centers were excluded.

MAIN OUTCOME MEASURES: Kaplan-Meier survival curves were used to estimate the event-free (EFS) and overall survival (OS) rates of the patients.

SAMPLE SIZE: 22.

RESULTS: Of the 22 children, 4 (18.2%) were less than three years old. All intracranial ependymomas had upfront surgical resection of the primary tumor. Gross total resection was achievable in 9 (42.9%) cases and subtotal resection in another 9 (42.9%). Near-total resection was done in 3 (14.3%) cases. Median time from surgery to start of radiotherapy was 62 days. RT was given to 17 (77.3%) patients. Both mean and median RT dose was 55.8 Gy. Only 5 (22.7%) of the children received chemotherapy. The median duration of follow-up was 5.38 years and the median time for EFS was 2.27 years. The cumulative OS rate of the study was 44.5%. The cumulative EFS survival rate of the study was 18.6%. Among demographic, pathological, radiological features, none had a statistically significant effect on the survival.

CONCLUSIONS: The outcomes are comparable to those reported by international investigators for similar populations. Further improvements can be achieved by avoiding delays in radiation therapy and adding molecular staging.

LIMITATIONS: The limited number of cases, retrospective nature, lack of molecular biology and size of the tumors.

CONFLICT OF INTEREST: None.

The peak age for pediatric ependymoma ranges from 0 to 4 years.[1] According to the 2007 World Health Organization (WHO) classification, the ependymal tumor is classified from Grade I to Grade III and ependymal radial glial cells are thought to be the precursor cells.[2,3] Although no formal staging system has been adapted so far, ependymoma can be subdivided into supratentorial (ST), posterior fossa (PF), and spinal tumors.[4] In children, infratentorial ependymomas are more frequent than supratentorial ependymomas (70% versus 30%, respectively).[5] Over 90% of childhood ependymomas arise intracranially and less than 10% arise within the spinal canal.[4] The best modality of treatment in pediatric ependymoma is radical surgery, followed by focal radiation therapy.[6] Gross total resection (GTR) is linked with the best outcome and is achievable in about 73% of pediatric ependymomas.[6,7] On the other hand, subtotal resection (STR) is an independent poor prognostic factor.[8] There is no evidence for the use of adjuvant chemotherapy. However, pre-irradiation cisplatin-based chemotherapy has a demonstrated a survival advantage in the near-totally resected pediatric ependymal tumor in some studies.[9,10] Due to long-term complications associated with cranial irradiation in younger children, postoperative chemotherapy to postpone or eliminate the need for radiotherapy (RT) has been evaluated by many investigators especially in patients whose brains are more susceptible to the adverse effects of radiation therapy.[11-13] With postoperative conformal radiation therapy (CRT) for localized childhood ependymoma, 7-year estimates of EFS and overall survival are 69·1% and 81.0%, respectively.[6] Long-term survival for pediatric ependymoma is approximately 57%.[14] Patients with recurrent ependymomas have a poor outcome for all age groups. Overall, 5-year survival for relapsed intracranial ependymoma is 24% to 27%.[15]

There has been no study on the characteristics and outcome of pediatric intracranial ependymoma from King Fahad Medical City (KFMC). In the present study, we investigated the characteristics of pediatric intracranial ependymoma and treatment outcome with surgery, RT and chemotherapy in a tertiary center in Saudi Arabia. Also, we identified the importance of the timing of RT. A large multicenter study of this tumor is needed to fully understand the outcome of this rare tumor in Saudi Arabia.

PATIENTS AND METHODS

This study was conducted at the Comprehensive Cancer Centre of KFMC, Riyadh. Retrospective data on intracranial ependymoma cases diagnosed between January 2006 and December 2015 were collected from electronic medical records after obtaining institutional review board approval. Pediatric ependymoma diagnosed and graded according to the WHO 2007 classification and those fulfilling the inclusion criteria were included in this study.[16] All tissue samples were reviewed by a neuropathologist at the institution to confirm the diagnosis of ependymoma. Demographics (age, sex), pathological (tumor subtype, tumor grade, cellularity, necrosis, microvascular proliferation and mitoses) and cerebrospinal fluid (CSF) cytology, surgery extents, postsurgery complications, time to start and type of RT, total dose and a fraction of RT, pre-RT chemotherapy, protocol and drugs used, the reason for giving chemotherapy, the toxicity of chemotherapy, response to therapy and duration of survival were recorded on a case report form and then uploaded on spreadsheets. We requested omission from the requirement for patient consent. The research used data from medical records and archival tissue slides for review, and there was no need for written informed consent.

All the pediatric patients (<14 years of age) with intracranial ependymoma were included in the study only if all modalities of treatment, surgery, radiation therapy and chemotherapy were done at KFMC at the time of diagnosis. Patients with prior radiation, chemotherapy, or surgical resection at other institutes were excluded. Patients with spinal or relapsed intracranial ependymoma at time of diagnosis were also excluded.

The goal was to study the characteristics of pediatric ependymoma and treatment modalities in a tertiary centre in Saudi Arabia. GTR was defined as intraoperatively assessed complete macroscopic resection with no evidence of residual tumor on magnetic resonance imaging (MRI). Near-total resection (NTR) was defined as <5 mm residual tumor in the greatest dimension on postoperative neuroimaging. All other cases were included as supratentorial. Event-free survival (EFS) was defined as the minimum interval from the time of diagnosis to the time of tumor recurrence, progression, death, second malignancies or the last follow-up. Overall survival (OS) defined as the interval from the date of diagnosis to the time of death or lost to follow-up for more than one year and last follow up.[6]

Baseline and demographic characteristics are presented in frequencies and percentages. All continuous variables are expressed as mean and standard deviation (SD) or median and range. The evaluation of primary ends points and outcome with complete follow up assessment of the study was evaluated by the difference in response rate treated by surgery and radiation therapy. Kaplan-Meier survival curves (including 95% confidence intervals and number at risk by strata) were used to esti-

mate the EFS and OS rates of the patients. The log-rank test was used to compare survival times between groups. A *P* value of <.05 was considered statistically significant. All data were analyzed using IBM SPSS (Armonk, New York, United States: IBM Corp) version 22.

RESULTS

Twenty-two patients met the inclusion criteria. The median age at presentation was 4 years (range 1-9 years). Most of the patients (81.8%, n=18) were three years of age or older, and 4 (18.2%) were younger than three years of age at the time of diagnosis. The male-to-female ratio was 13:9 (59.1-40.9%). Pre-operative MRI of the spine was conducted in 19 out of 22 patients to check for spinal metastasis while postoperative MRI for residual disease was done in all patients except one. MRI detected spinal metastasis in 7/19 (36.8%) patients and the remaining three did not have spinal MRI. Follow-up computed tomography (CT) brain and/or MRI examination of the brain/spine was done to check for post-operative complications, the response of the disease to different modalities of treatment, and disease recurrence. Lumbar puncture to detect malignant cells by CSF cytological analysis was done in 12 (54.5%) patients. The median interval from surgery to CSF sampling was 24 days. None of these patients had malignant cells in the CSF. In a bivariate analysis of the demographic, pathological, radiological features, none of the parameters had a statistically significant effect on survival (**Table 1**).

Table 1. Demographic, pathological, radiological features of the participants (n=22).

Characteristics	Alive	Dead	*P* value
Age group			
<3	2 (20.0)	2 (16.7)	.8
≥3	8 (80.0)	10 (83.3)	
Gender			
Male	7 (70.0)	6 (50.0)	.737
Female	3 (30.0)	6 (50.0)	
WHO Grade			
2	1 (10.0)	3 (25.0)	.396
3	9 (90.0)	9 (75.0)	
Cellularity			
High	9 (90.0)	6 (50.0)	
Moderate	1 (10.0)	4 (33.3)	.319
NA	0 (0.0)	2 (16.7)	
Necrosis			
Absent	1 (10.0)	0 (0.0)	
NA	0 (0.0)	2 (16.7)	.358
Present	9 (90.0)	10 (83.3)	
MVP			
Absent	1 (10.0)	0 (0.0)	
NA	0 (0.0)	2 (16.7)	.358
Present	9 (90.0)	10 (83.3)	
Mitoses			
<5	3 (30.0)	3 (30.0)	.949
>5	7 (70.0)	7 (70.0)	
Radiological location			
ST	4 (40.0)	4 (33.3)	.502
IT	6 (60.0)	8 (66.7)	
Hydrocephalus			
No	2 (20.0)	4 (33.3)	.8
Yes	8 (80.0)	8 (66.7)	
Calcification			
No	4 (40.0)	6 (50.0)	.138
Yes	6 (60.0)	6 (50.0)	

Data are n(%).

Surgical resection

All children with intracranial ependymoma underwent a first surgical resection of the primary tumor. GTR was possible in 9 (42.9%), NTR in 3 (14.3%) and STR in 9 (42.9%) patients. In one patient, there was no postoperative MRI to define the extent of surgical resection. Fifteen of twenty-two (68.2%) patients underwent a second surgical resection for recurrent ependymoma. Out of 10 surviving patients, 4 cases had GTR, 4 cases STR and 1 case NTR at the time of presentation. In the remaining patient, there was no postoperative MRI. Six of the 10 surviving patients experienced disease relapse, and resection showed that two cases had GTR, two had NTR, and one had STR at a second surgery. For one patient, there was no available data as her second surgery was done in Germany.

Radiotherapy

RT was given to 17 (77.3%) patients. The focal to craniospinal irradiation (CSI) ratio was 10:7 (45.5-31.8%). Out of 7 patients with spinal metastasis at diagnosis, only 4 received CSI at median doses of 55.8 Gy, two did not

Table 1 (cont). Demographic, pathological, radiological features of the participants (n=22).

Characteristics	Alive	Dead	*P* value
Extension through foramen Luchka/ Magendie			
No	8 (80.0)	9 (75.0)	.8
Yes	2 (20.0)	3 (25.0)	
Necrosis			
No	5 (50.0)	8 (66.7)	.28
Yes	5 (50.0)	4 (33.3)	
Intratumoral hemorrhage			
No	8 (80.0)	7 (58.3)	.8
Yes	2 (20.0)	5 (41.7)	
Cyst			
No	5 (50.0)	6 (50.0)	.999
Yes	5 (50.0)	6 (50.0)	
Spinal mets			
No	6 (60.0)	9 (75.0)	.502
Yes	4 (40.0)	3 (25.0)	

Data are n (%).

receive RT because of age at presentation and the parents refused RT in one child. Among children with spinal metastasis, all received focal RT except two who gained CSI. Median and mean time from surgery to starting RT was 62.00 and 118.9 days, respectively. Both mean and median RT dose was 55.8 Gy.

Chemotherapy

Only 4 (18.18%) children received chemotherapy; 3 were younger than 3 years of age and had received infant BT2 protocol whereas one patient was 4 years old and was treated with the SK-HIT-2000 protocol. Among those treated with chemotherapy, two of the patients were surviving at the time of writing.

Treatment outcome

The median duration of follow-up for the cohort was 5.38 years and the median time for EFS was 2.27 years. The cumulative OS rate of the study was 44.5%. The cumulative EFS survival rate of the study was 18.6%; the Kaplan-Meier curve is shown in **Figure 1**. The remaining figures are comparisons of the survival curves for the first surgeries (**Figure 2**), the second surgeries (**Figure 3**), the radiation types (**Figure 4**), presence of spinal metastasis (**Figure 5**), and age groups (**Figure 6**). The corresponding median duration of follow-up (years) and survival rates for OS and EFS are shown in **Table 2a-c**.

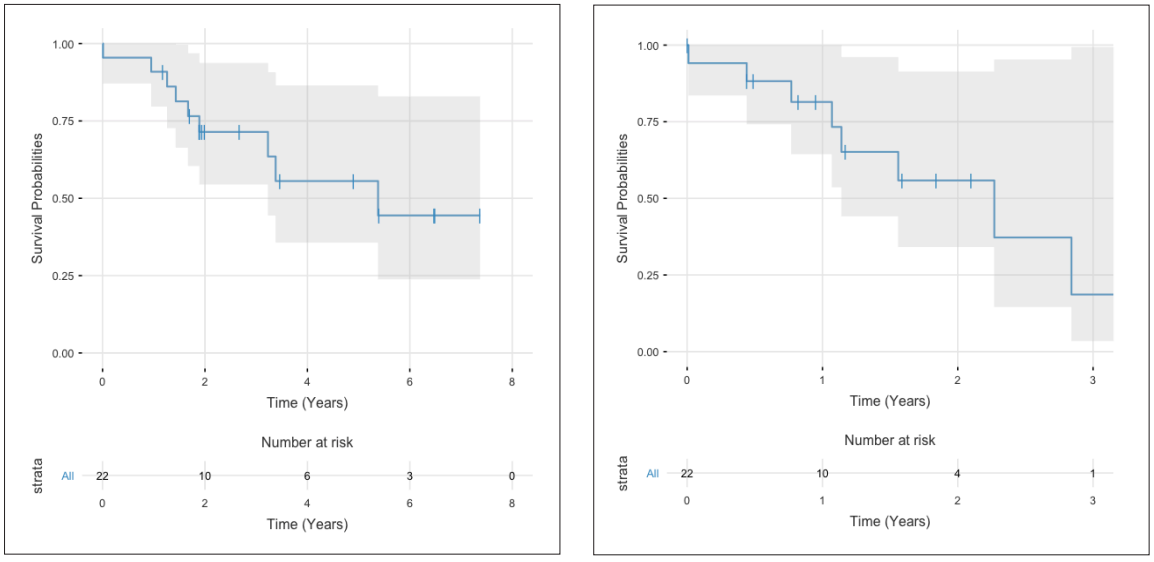

Figure 1. Overall survival (left) and event-free survival (right) for all patients (n=22).

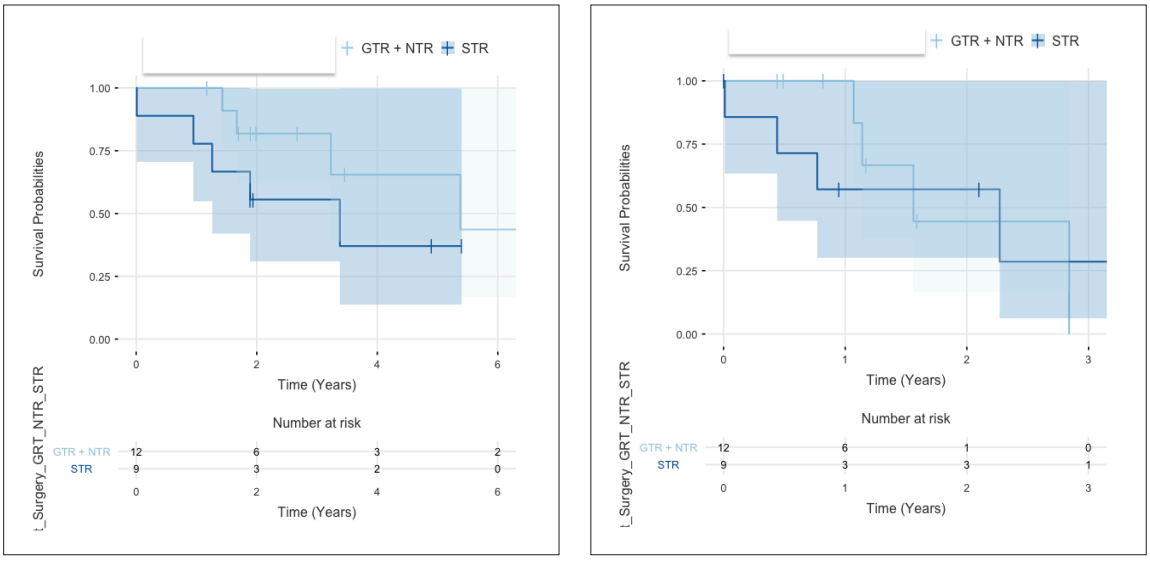

Figure 2. Overall survival (left) and event-free survival (right) for gross total resection plus near-total resection vs subtotal resection during the first surgery.

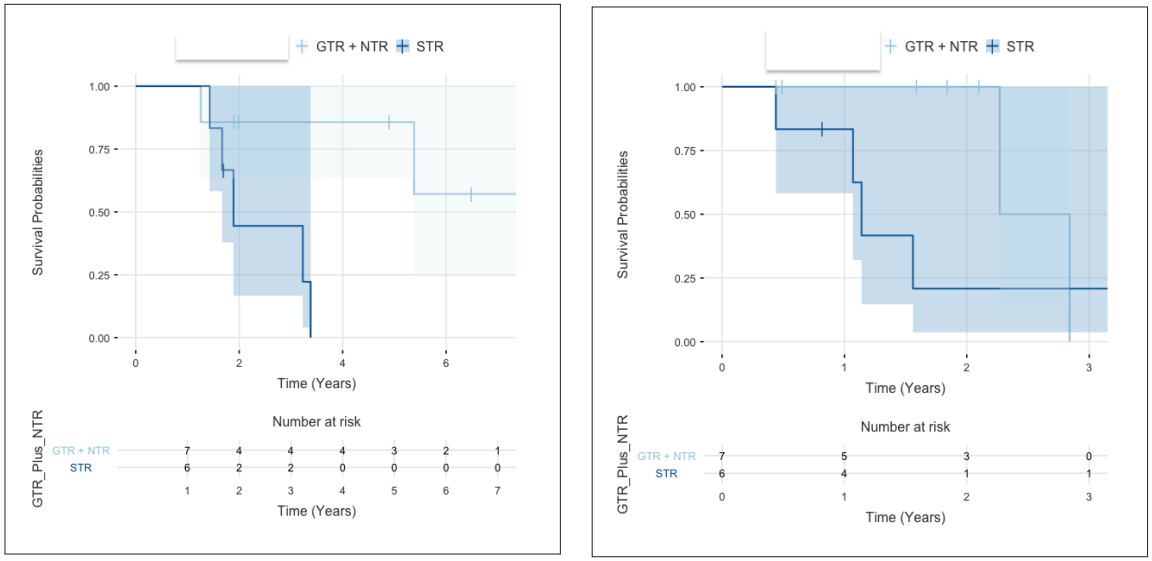

Figure 3. Overall survival (left) and event-free survival (right) for gross total resection plus near-total resection vs subtotal resection during the second surgery.

Table 2a. Follow-up and survival after first and second surgery.

	Median follow-up (years)		Overall survival	*P* value	Event-free survival	*P* value
	OS	EFS				
First surgery						
GTR+NTR	5.38	1.56	43.6%	.278	44.4%	.788
STR	3.38	2.27	37.0%		28.6%	
Second surgery						
GTR+NTR	5.92	2.27	57.1%	.019	50%	.177
STR	1.89	1.40	22.2%		20.8%	

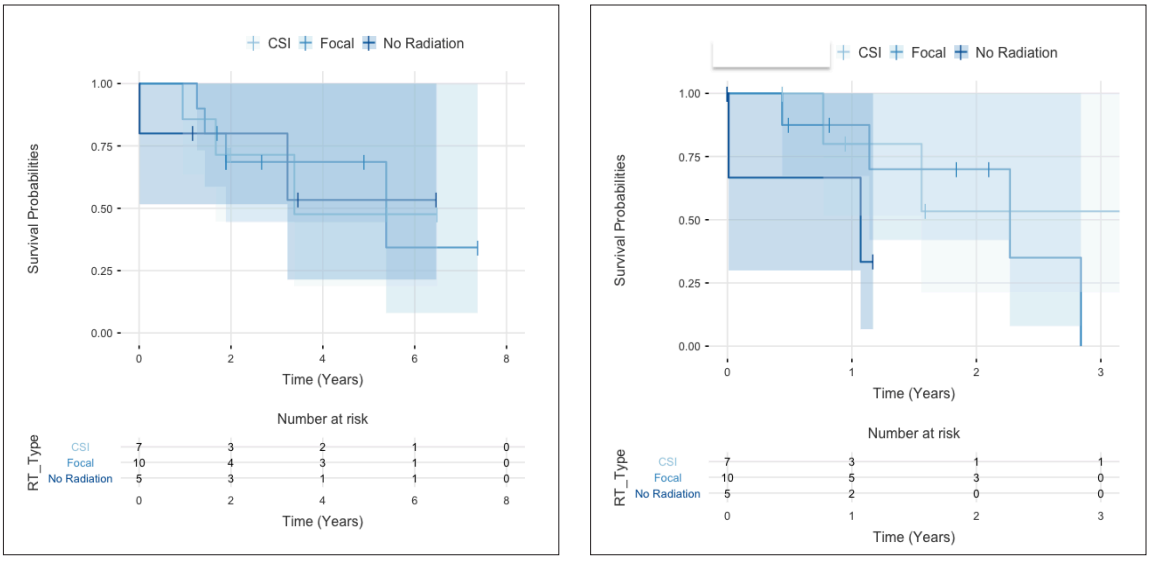

Figure 4. Overall survival (left) and event-free survival (right) for focal radiation, craniospinal irradiation and no radiation.

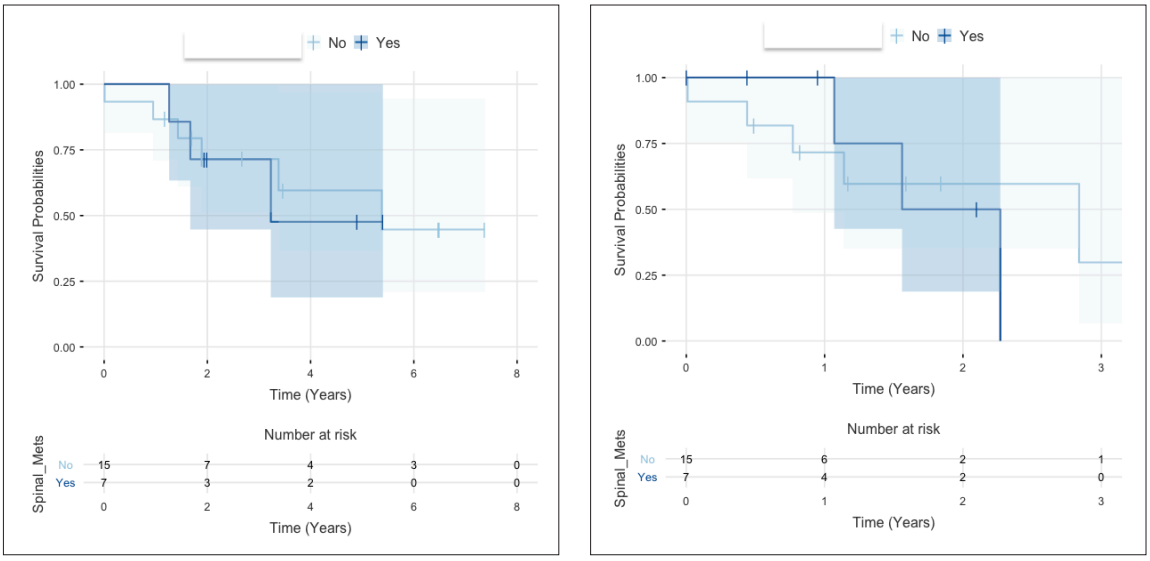

Figure 5. Overall survival (left) and event-free survival (right) for patients with and without spinal metastases.

Table 2b. Follow-up and survival by type of radiotherapy and by presence of spinal metastases.

	Median follow-up (years)		Overall survival	*P* value	Event-free survival	*P* value
	OS	EFS				
Radiation therapy type						
Focal	5.38	2.27	34.3%		35%	
Craniospinal irradiation	3.38	3.38	47.6%	.996	53.3%	.285
No irradiation	4.31	1.07	53.3%		33.3%	
Spinal metastasis						
Yes	3.23	1.56	47.6%	.898	50.0%	.758
No	5.38	2.84	44.7%		29.8%	

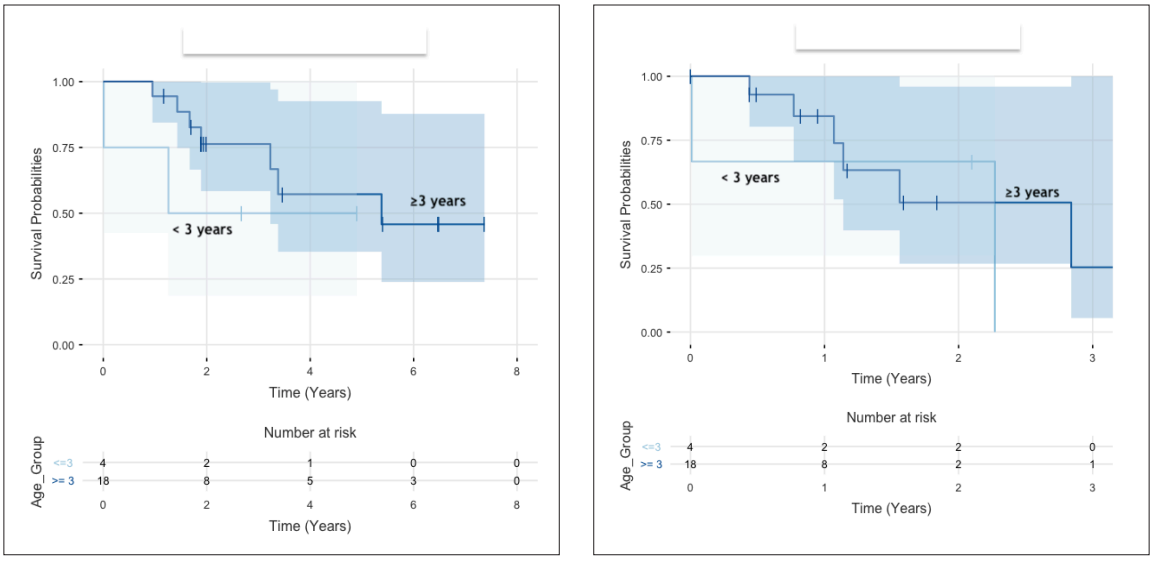

Figure 6. Overall survival (left) and event-free survival (right) by age group (<3 years and ≥3 years).

Table 2c. Survival and follow-up by age group.

	Median follow-up (years)		Overall survival	*P* value	Event-free survival	*P* value
	OS	EFS				
Age group						
<3 years	1.26	1.56	50.0%	.340	66.0%	.637
≥3 years	5.3	2.27	45.8%		25.3%	

DISCUSSION

To our understanding, this is the first such study from Saudi Arabia to describe the demographic characteristics and outcome of pediatric intracranial ependymoma patients treated with different treatment modalities at a single center. The median duration for follow-up was 5.38 years and the median time for EFS was 2.27 years. The cumulative OS rate of the study was 44.5%. The cumulative EFS survival rate of the study was 18.6%. The results of our study are at least comparable to those reported by a multicenter trial of the French Society of Pediatric Oncology (2001).[11] In European trials, the 4-year progression-free and overall survival was reported to range from 30-60% and 60-80% respectively.[16] According to Surveillance, Epidemiology and End Results (SEER-17) database from 1973 to 2003, the five-year survival for intracranial ependymoma was 57.1% -59.5%.[14] Comparison with our results is difficult because of the limited number of cases in our study. In the present study, GTR/NTR was possible in 57.2% of patients because almost all cases were anaplastic ependymoma in the posterior fossa, which is a challenge to achieve total resection due to the infiltrative nature, size, and brainstem involvement that might explain lower GTR/NTR. GTR/ NTR, as compared to STR, was associated with a better outcome. Surgical resection has been proven to be a prognostic factor of outcome in the SFOP (65%) and AIEOP (69%) trials, but not in the CNS9204 (51%) and CNS9904 (39%) trials.[17]

In this study, the overall rates of EFS with focal, CSI and no radiation were 35%, 53.3% and 33.3% respectively. The OS with focal, CSI and no radiation rates are 34.3%, 47.6% and 53.3% respectively. In the study of Merchant TE et al, 107 patients treated with immediate postoperative conformal radiotherapy (without delay or chemotherapy), 7-year, EFS, and overall survival were 76·9% and 85·0% respectively.[6] These differences might be due to more cases with localized disease, GTR (125/153) and earlier start of CRT (median time to start RT was of 1.5 month) in that report. As compared to their data, in our study, the median and mean time to start RT was 62.00 and 118.9 days, respectively and only 4 out of 7 patients with spinal metastasis at diagnosis received CSI. Almost all cases with the advanced

disseminated anaplastic ependymoma and hydrocephalus that reflect a large tumor size show that the outcome of the study is comparable to those reported by international investigators for such population. In the same study, 5 years EFS and OS for those who had both STR or NTR was 41·% and 52·4% respectively that is only slightly superior to our cases that had STR excluding NTR (EFS was 28.6% OS was 37%). A total of 17 out of 22 patients in our study received CRT, but due to a small number of patients who went without CRT, no conclusion could be drawn from these two groups. Only 5 (22.7%) children received chemotherapy and only two of these patients were alive until the time of data collection. Due to a small number of patients, it is difficult to conclude the outcome after chemotherapy. The effect of chemotherapy on survival has been documented in many studies.[9,11,12]

In our study, the bivariate analysis showed no prognostic significance for any of the demographic, pathological or radiological features in intracranial ependymoma. Due to the small sample size, the non-statistically significant *P* values for survival could also be due to the Type 2 error. SEER-17 data (1973-2003) showed the 5-year survival to be almost identical for supratentorial and infratentorial ependymoma (59.5% vs 57.1%.[14] Patients under the age of 3 years at the time of CRT had a higher risk of local failure compared to older patients. Similar results were also reported by various other studies.[8,14] For children younger than 3 years of age, our results are almost similar to other international trials. In HIT-SKK 87-9, 3-year PFS and OS were 27.3% and 55.9% respectively. In SFOP, 4-year PFS was 22% and 4-year OS was 59%. In HEADSTART III, 19 children were less than 10 years and for infratentorial ependymoma, 3-year EFS was 27% and 3-year OS was 73%.[18] In this study, the male to female ratio was similar to the trial reported by Cage.[8] PF location was more common (63.6%) as compared ST (36.4%) and almost similar findings have been reported previously.[4]

Two studies have been reported from the Middle East; in one study of 73 patients, 53 tumors were located in the posterior fossa. Patients who had GTR, NTR, and partial resection were 46.3%, 11.9% and 41.8% respectively. The 3-year PFS was 59.5% and the 3-year OS was 61% but the number of cases with anaplastic histology were only 28 as compared to our study where most of th etumors were of anaplastic histology.[19] In another study of 40 patients, the 5-year PFS rate was 50.8% and OS rate was 64.9%. GTR was done in 50% and STR in 45% and again children with anaplastic ependymoma were only 22(55%).[20]

The limited number of cases, retrospective nature, lack of molecular biology and size of the tumors were limitations of our study. In conclusion, this study is the first of its kind in Saudi Arabia. It describes characteristics and the outcomes of 22 childhood cases of intracranial ependymoma treated with surgical resection followed by radiotherapy or chemotherapy. The characteristics and outcomes of patients and tumors were comparable to those reported by other international investigators. Almost all cases had advanced disseminated anaplastic ependymoma and hydrocephalus, which reflects a large tumor size. Further improvements can be achieved by avoiding delays in radiation therapy and adding molecular staging in the future. A larger multicenter study throughout the country would provide more definitive information on this rare tumor.

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