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Original Investigation

Survival Benefit with Gross Total Resection and Adjuvant Radiotherapy in Childhood Atypical Teratoid/Rhabdoid Tumors: Results of a Single-Center Cohort of 27 Cases

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ABSTRACT

AIM: To share a single center experience with 27 atypical teratoid/rhabdoid tumor (AT/RT) cases, and to determine the effect of gross total tumor resection and other clinical characteristics on the overall survival rate of AT/RT.

MATERIAL and METHODS: We included 27 patients—with a histopathologically confirmed primary intracranial childhood AT/RT—who were operated in our clinic between January 2000 and December 2017. Age, sex, tumor location, disseminated disease, the presence of hydrocephalus, symptom duration till diagnosis, the extent of resection, and adjuvant radiotherapy were evaluated for their influence on overall survival.

RESULTS: Median age at diagnosis for 27 patients was 19.1 months (7.2 months-5 years). Gross total resection was possible in 13 (48.72%) patients. Except for three patients who died of perioperative complications, all patients received chemotherapy and 11 received radiotherapy. In univariate analysis, male sex, older age at diagnosis (≥24 months), gross total resection, and radiotherapy were associated with overall longer survival; however, radiotherapy remained the only significant parameter in multivariate analysis.

CONCLUSION: AT/RT is a rare and dreadful brain tumor that has low survival rates despite contemporary treatment. Radiotherapy seems to prolong survival; however, large-scale studies are needed to establish prognostic factors.

KEYWORDS: Brain neoplasms, Childhood, Observational study, Rhabdoid tumor

INTRODUCTION

Atypical teratoid/rhabdoid tumor (AT/RT) of childhood is a rare and aggressive tumor. Although it constitutes less than 2% of all pediatric CNS tumors, it is the most common malignant CNS tumor under one year of age (13,24). Approximately 66% of cases presenting with this tumor are under two years of age, and AT/RT constitutes up to 20% of all childhood CNS tumors in patients younger than three years (14,34).

Several first-phase I/II trials are ongoing that employ agents designed explicitly for rhabdoid tumors targeting molecular defects. However, surgery, chemotherapy, and radiation are still the mainstay of treatment (13). Despite multimodal treatment including surgery followed by chemo-radiotherapy, less than 50% of cases remain alive at the end of the first year after diagnosis, and the five-year survival rate is as low as 28% (24). Influence of chemotherapy and radiation therapy on overall survival in this dreadful tumor is almost

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indisputable. There are a few single and multi-center series that explored the influence of prognostic factors on survival, and some of these looked at the effect of extent of resection (2,8,10,16,19,31,33,35).

In this study, we aim to share our experience with single-institution 27 patients diagnosed with primary intracranial AT/RT and determine the effect of gross total tumor resection and other clinical characteristics on overall survival of AT/RT.

MATERIAL and METHODS

Study Population

In this study, we included 27 patients with a histopathologically confirmed primary intracranial AT/RT who were operated in our clinic between January 2000 and December 2017, and under 18 years of age at the time of diagnosis. Patient charts, discharge notes, radiology and pathology reports, and follow-up notes in our pediatric oncology clinic were analyzed in a retrospective manner. When the follow-up visits were conducted outside our clinic, telephonic interview was conducted to ascertain the final status of the patients.

Clinical and Radiological Data

Sex, age at the time of diagnosis, symptoms at admission, neurologic status, radiologic findings, the extent of resection, the presence of disseminated disease, and need for CSF diversion were recorded. All patients had preoperative cranial MRI at least consisting of three-planar T1 weighted, axial T2 weighted, and post-contrast axial T1 weighted images. A post-op MRI scan was performed in all patients within 48 hours postoperatively unless the patient was critically ill. Fluid-attenuated inversion recovery and diffusion-weighted images were available for patients who were operated after 2007. When MRI was not available, an early postoperative CT scan was performed to rule out surgical site hematoma and to document the extent of resection. Gross total resection (GTR) was defined as the absence of any visible residual tumor in the immediate postoperative MRI or CT scan. The extent of resection was regarded as either subtotal excision/biopsy if there was any sign of a radiologically-apparent residual tumor. Histopathological evaluation was based on the "The WHO Classification of Tumors of the Central Nervous System".

Surgical Treatment, Adjuvant Therapy, and Survival

Maximum safe resection was the goal of all surgical interventions. Postoperatively, all patients were followed up by a team of neurosurgeons, pediatric oncologists, and radiation oncologists. Adjuvant therapy consisted of various combinations of chemotherapeutic agents depending on the best available data at the time of treatment. For patients older than three years of age, radiotherapy was added to the treatment protocol. Overall survival was calculated as the duration between the time of diagnosis and time of death with censoring at the last follow-up for patients who were alive and for patients who were lost to follow-up. The exact date of out-of-hospital deaths was acquired using a web-based government service (www.obs.gov.tr).

Statistical Analysis

SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was used for statistical analysis. Means and standard deviations were calculated for parametric and normally distributed data. For non-parametric data or when data were not normally distributed, medians (range) were used whereas categorical data were presented as percentages. Survival analyses were performed using the Kaplan-Meier method. The log-rank test was used for comparison of subgroup outcomes. Cox proportional hazard model was used for multivariate analysis. A p-value lower than 0.05 was considered statistically significant.

RESULTS

Demographic Data

Clinical characteristics of patients are given in Table I. There were 27 patients (15 females, 12 males) in the study. The median age of patients at the time of diagnosis was 19.1 months (range 0–194.2). Only eight patients (29.6%) were older than 36 months of age at admission and the distribution of children below and over 24 months of age was 14 and 13 patients respectively. Tumor location was supratentorial in 15 (55.6%) and infratentorial in 12 (44.4%) patients.

Symptoms and Clinical Features

One patient had a prenatal diagnosis of the tumor. Excluding this patient, the duration of signs and symptoms of patients ranged between seven days and six months (median 30 days). Signs and symptoms of patients are summarized in Table II. Hydrocephalus was the most common finding followed by ataxia, headache, and nausea/vomiting.

Radiologic Characteristics

The distribution of tumor location in the infratentorial compartment was as follows: tumor was seen occupying the fourth ventricle in three patients, main bulk of the tumor was situated in cerebellar hemispheres in four patients, and the cerebellopontine angle was occupied in three patients owing to tumors arising from middle cerebellar peduncle. One mesencephalic tumor was seen invading left crus cerebri. A midline cerebellar tumor extending to the pineal region through tentorial incisura was found in the infratentorial group. The tumor locations in the supratentorial compartment were as follows: four hypothalamic-chiasmatic tumors extending to the suprasellar cistern, one inside the third ventricle, six in cerebral hemispheres, one insular, one in pineal region, and two temporal intra-axial tumors extending extra-axially to invade meninges.

Pronounced contrast enhancement was noticed in 83.3% of cases (Figure 1A-F). Contrast enhancement was heterogeneous in most of the cases, and only a few showed homogeneous contrast enhancement. In three patients tumor showed slight contrast enhancement. In one patient, tumor in the cerebellopontine angle did not show enhancement at all after administration of contrast. In 11 cases, the signal

intensity of the tumor was heterogeneous owing to mixed solid and cystic components.

Hydrocephalus was a prominent finding, particularly with large tumors. Five of the infratentorial tumors and four supratentorial tumors manifested with hydrocephalus at the time of diagnosis. Tumor location was fourth ventricle (n=3), midline cerebellar, and left middle cerebellar peduncle for infratentorial lesions resulting in hydrocephalus. Regarding supratentorial tumors, those occupying suprasellar region (n=2), pineal region, and left cerebral hemisphere caused hydrocephalus.

At the time of presentation, nodular or diffuse pial enhancement helped discern disseminated disease in 10 (37.0%) patients (Figure 2A, B).

Table I: Clinical Characteristics of Study Cohort

Case #	Sex	Age at diagnosis (months)	Duration of symptoms (days)	Tumor location	GTR	Adjuvant Rdtx	Follow-up (months)	Complication	HCP Treated with V/P shunt	Outcome
1	M	194.2	15	S	+	+	50.0	-	-	Dead
2	M	83.4	105	I	+	+	106.1	Mutism	-	Dead
3	F	116.1	30	S	+	+	186.0	-	-	Alive
4	F	12.0	51	I	+	-	17.6	CSF fistula	-	Dead
5	M	31.6	10	I	-	-	5.3	-	-	Dead
6	M	40.5	7	S	+	+	186.5	-	-	Alive
7	F	12.5	10	S	-	-	3.7	-	-	Dead
8	M	5.8	30	I	-	+	27.8	CSF fistula	-	Lost to follow-up
9	M	18.5	180	I	-	+	7.6	-	-	Lost to follow-up
10	F	6.2	20	I	+	-	5.1	-	-	Dead
11	F	26.8	15	I	-	-	5.3	-	-	Dead
12	F	4.9	45	S	-	-	0.1	Periop mortality	-	Dead
13	F	5.0	15	S	-	-	4.9	CSF fistula	+	Dead
14	F	31.3	10	I	-	-	5.2	Mutism	-	Dead
15	M	114.6	30	S	+	+	57.2	-	-	Alive
16	M	81.8	180	S	-	+	4.5	-	-	Dead
17	F	0.5	7	I	-	-	4.8	CSF fistula	-	Dead
18	F	41.8	150	S	+	+	5.6	-	+	Dead
19	F	7.2	60	I	+	-	7.2	-	+	Dead
20	F	19.1	30	S	+	-	8.5	-	-	Dead
21	M	24.9	15	S	+	+	15.3	-	+	Dead
22	F	8.9	60	I	+	-	0.2	Periop mortality	-	Dead
23	M	9.3	10	S	-	-	0.5	Periop mortality	-	Dead
24	M	0.0	Prenatal	S	+	-	5.8	-	-	Dead
25	F	8.2	15	I	-	-	7.1		+	Dead
26	M	37.0	150	S	-	+	21.7	-	+	Dead
27	F	29.8	90	I	-	-	9.4	Mutism	+	Dead

CSF: *Cerebrospinal fluid,* ***F:*** *female,* ***GTR:*** *Gross total resection,* ***HCP:*** *Hydrocephalus,* ***I:*** *Infratentorial,* ***M:*** *Male,* ***Rdtx:*** *Radiotherapy,* ***S:*** *supratentorial,* ***V/P:*** *Ventriculo-peritoneal.*

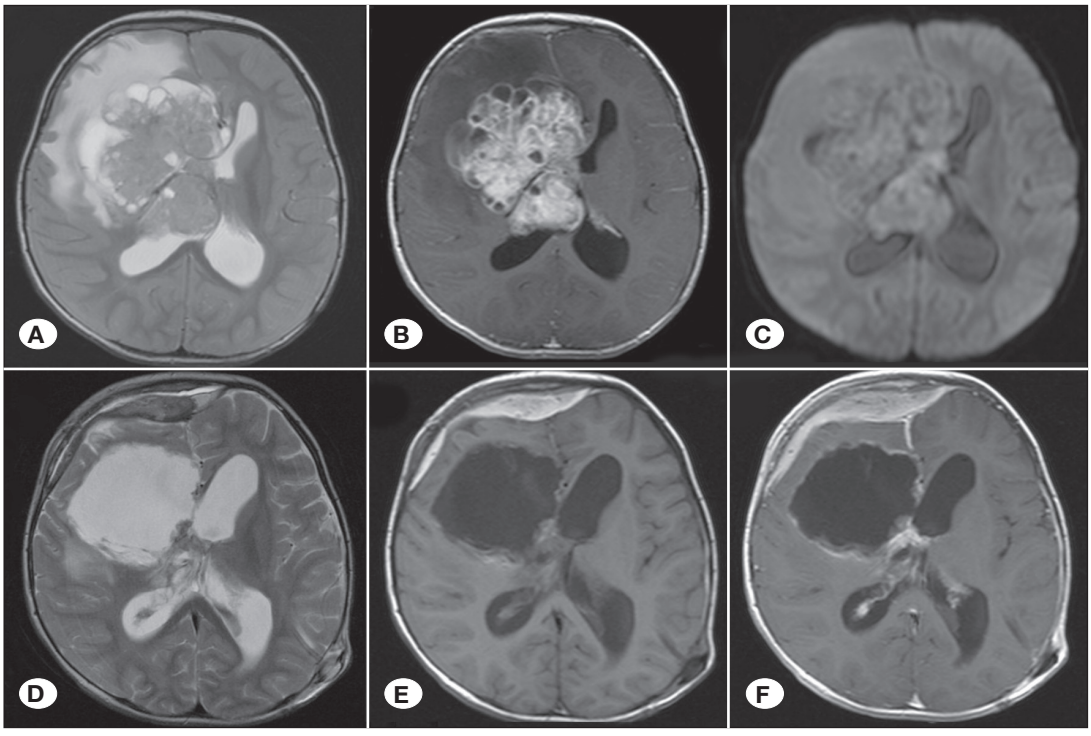

Figure 1: Preoperative and postoperative MRI scans of patient number 21 in Table 1. T2 weighted axial MR image shows a frontal intraparenchymal tumor. Tumor infiltrates right lateral ventricle and posterior part of third ventricle. There is significant peritumoral white matter edema in right frontal lobe which is demonstrated with hyper-intense signal changes **(A)**. Tumor enhances heterogeneously after intravenous contrast agent administration. The solid central part is accompanied by numerous cystic structures on the periphery **(B)**. Tumor shows high signal intensity on diffusion-weighted images, due to tumor's high nucleus-cytoplasm ratio and hypercellularity **(C)**. Postoperative T2 weighted **(D)**, pre-contrast T1 weighted **(E)** and T1 weighted contrast enhanced **(F)** axial MR images show gross total tumor excision. Ventriculoperitoneal shunt reservoir and part of ventricular catheter may also be seen on the left side in these images **(D, E, F)**.

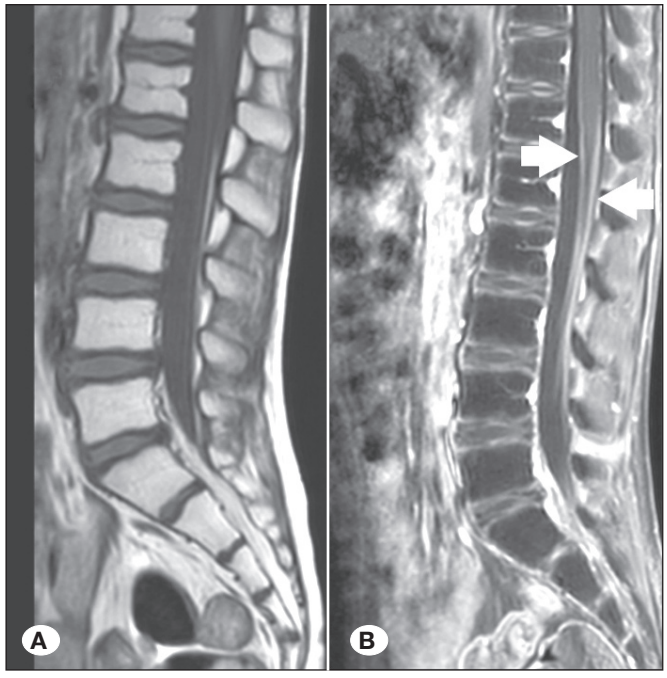

Figure 2: Pre-contrast T1 weighted **(A)** and post-contrast fat suppressed sagittal images **(B)**. Arrows point to pial enhancement which indicates tumor seeding **(B)**.

Histopathologic Features

On light microscopic examination, the tumors exhibited distinct cellular components. Rhabdoid cells were characterized with eccentrically located vesicular nuclei and clear, sometimes eosinophilic cytoplasm. Another component of the tumor was spindle-shaped mesenchymal cells along with small islands of primitive neuroectodermal foci. Cells showed pronounced pleomorphism and mitotic activity. Ki-67 index was high. Necrosis was a common finding in all specimens; however, histological evidence of focal calcification was observed in only 22.3% (n=6) of tumors. Definitive diagnosis was based on loss of INI1 expression in all tumor samples. Specimens showed immunoreactivity for vimentin in 74.1% of cases. Smooth muscle actin (SMA), epithelial membrane antigen (EMA), and glial fibrillary acidic protein immunoreactivity were observed in 70.4%, 66.7%, and 29.6% of cases, respectively.

Surgical Treatment, Follow-up, and Outcome

GTR was achieved in 13 (48.2%) patients. Overall median survival duration for 27 patients was 7.1 months. Permanent ventricul operitoneal shunt insertion was performed in seven out of the nine patients who had hydrocephalus preoperatively. Temporary CSF diversion was performed using external ventricular drainage catheter in the remaining two patients. Six (22.2%) patients were operated twice due to either tumor

Table II: Symptoms and Signs at Admission

Symptom and Sign	n
Hydrocephalus	9
Ataxia/difficulty in walking	6
Headache	6
Nausea/vomiting	6
Eye deviation	4
Hemiparesis/limb weakness	3
Restlessness	2
Somnolence	2
Ptosis	2
Torticollis	2
Epileptic seizures	2
Diabetes insipidus	1
Diplopia	1
Loss of head control	1

recurrence (n=4) or residual tumor (n=2) identified on the postoperative radiologic study. Three patients (two with supratentorial and one with infratentorial tumor) died perioperatively owing to surgical complications, and immediate postoperative extubation was impossible in any of these three patients. Only one of the perioperative deaths was in the GTR group. Out of four patients who developed postoperative CSF fistula, two required wound revision, and the other two were managed conservatively. Three patients developed a brief period of cerebellar mutism after the resection of posterior fossa tumors possibly because ofa partial split of the inferior vermis. Postoperative chemotherapy regimen was initiated for all surviving patients. All the eight patients older than 36 months of age and an additional three patients who were younger at the time of diagnosis received adjuvant radiation therapy. Mean follow-up time for the 27 patients was 28.1 months.

Clinical characteristics, such as sex, patient age at the time of diagnosis, the location of the tumor, the extent of resection, adjuvant radiotherapy, duration of symptoms, the presence of disseminated disease, and hydrocephalus were assessed for their influence on overall survival. Two equal sized subgroups were formed by choosing 24 months as the cut-off value for

Table III: Clinical Characteristics and Median Survival Times

Variables	Median survival (months)	Univariate Analysis p	Multivariate Analysis p
Sex		**0.045**	0.869
Male	18.5		
Female	5.6		
Age at diagnosis		**0.039**	0.524
<24 months	5.4		
≥24 months	15.3		
Duration of symptoms		0.111	-
<1 month	5.3		
≥1 month	9.0		
Location of tumor		0.865	-
Infratentorial	7.2		
Supratentorial	5.8		
Extent of resection		**0.040**	0.167
Subtotal resection/biopsy	5.2		
GTR	15.3		
Hydrocephalus		0.105	-
Absent	9.0		
Present	5.1		
Adjuvant radiotherapy		**0.001**	**0.025**
No	5.3		
Yes	27.8		
Disseminated disease		0.968	-
No	7.1		
Yes	6.5		

patient age and 30 days as the cut-off value for the duration of symptoms. In univariate analysis, male sex, older patient age, gross total tumor resection, and administration of adjuvant radiotherapy were associated with improved survival (Table III). In multivariate Cox proportional hazards model with backward elimination for the prediction of overall survival, only adjuvant radiotherapy was shown to increase survival (Table III). Kaplan-Meier curve for the entire cohort and survival curves comparison for the subgroups are given in Figure 3.

At the end of the study period, three patients belonging to the gross total tumor resection and the adjuvant chemo-radiotherapy group were still alive with the recorded follow-up time of 57.2, 186.0, and 186.5 months.

■ DISCUSSION

An atypical teratoid/rhabdoid tumor is a rare disease with unfavorable outcome most commonly seen in children, although few cases of adult AT/RT have also been reported (20). Patient age at the time of diagnosis ranges between 7.2 months and 5 years (1,7,21,22,25,26,28); however, cases of in utero diagnosis have also been reported (4).

Intracranial location of AT/RT has been reported to be in the posterior fossa (~55%), in the supratentorial compartment (~40%), or pineal region (~5%) in many series (9,30). When in the posterior fossa, the tumor may invade cerebellar tissue, block fourth ventricular outflow, or it may grow exophytically from cerebellar peduncles to occupy the cerebellopontine angle—found in 11.1% of cases in our series. The distribution of supratentorial and infratentorial tumor cases in our study was 56.4% and 44.4%, respectively. Likewise, in a series of 15 AT/RT cases, Biswas et al. reported a higher number of supratentorial tumors (60% vs. 40%) (4). Hilden et al. published results of therapy in 42 children enrolled in a registry wherein they reported 61.9% supratentorial location (16). Additionally, the general literature reveals that these tumors are predisposed to cerebellar fossa (12,18).

Radiological findings of AT/RT are generally indistinguishable from PNET and medulloblastomas (11). Typical CT scan finding of AT/RT is increased-density solid mass due to tumor's high cellular content that enhances heterogeneously after contrast administration. In the magnetic resonance (MR) era, the benefit of performing cranial CT is debatable; however, it can help in accelerating a definitive diagnosis. Typical MR scan presentations of AT/RT are hypointense signals on T1-weighted images, hypo- or isointense signals on T2-weighted images, and heterogeneous contrast enhancement with areas of hemorrhage and necrosis (11). AT/RT is also characterized by restricted diffusion because of hypercellularity and neoplastic cells with high nuclear-to-cytoplasmic ratios and small extracellular spaces (21). Because these features are relatively typical for other tumors, such as PNET, medulloblastoma, and ependymoma, a definitive radiological diagnosis is often impossible. Most of the radiology reports in our study included AT/RT in the differential diagnosis and none identified AT/RT definitively.

Light microscopic characteristics of AT/RT include rhabdoid cells with eccentric round nuclei containing prominent nucleoli within a fibrillary or granular eosinophilic cytoplasm. There are sometimes small spindle-shaped rhabdoid cells with ovoid nuclei or large cells containing nuclei with wrinkled margins (5,30). AT/RT is so called because of the varying number of PNET cells, malignant mesenchymal spindle-shaped cells, and cells with epithelial differentiation accompanying the rhabdoid cells (29). AT/RT tumors have previously been mistaken for PNET-medulloblastomas because of their similar histological features. Therefore, a careful immunohistochemical workup is warranted (3). Positive reactions to neural antibodies, such

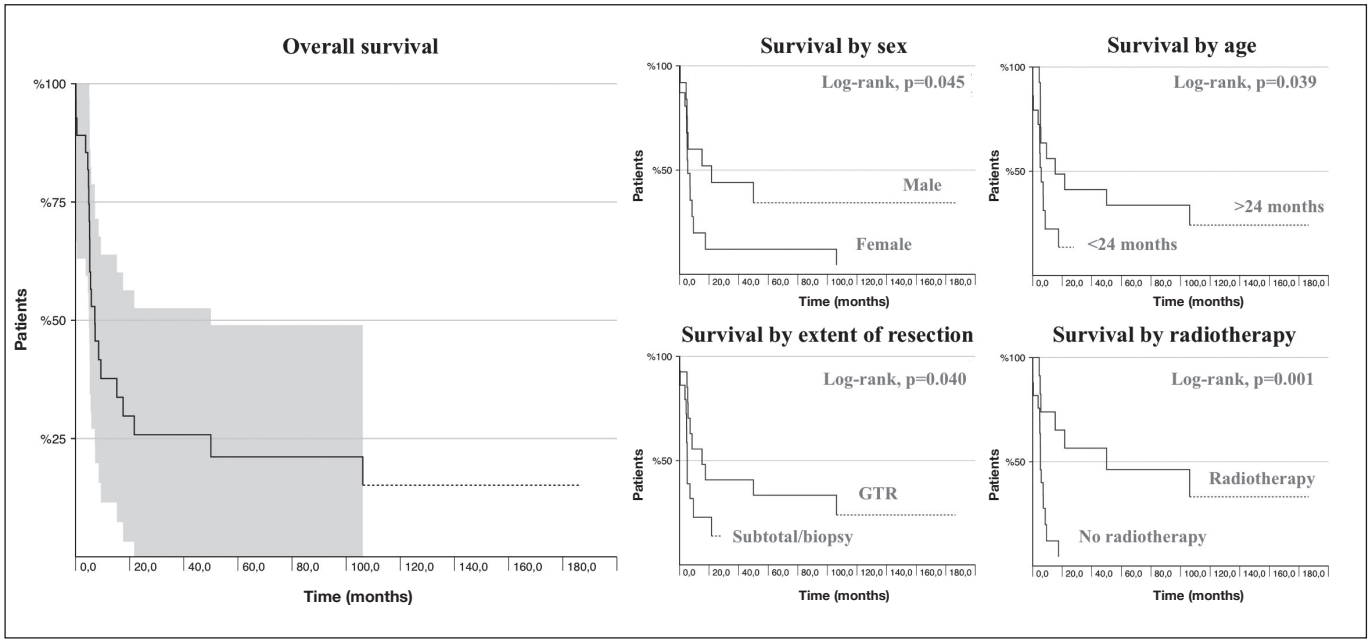

Figure 3: Kaplan-Meier curves for clinical characteristics (**GTR:** gross total resection).

as neurofilament protein and glial fibrillary acid protein, can be exhibitedin both PNET and AT/RT. Nevertheless, rhabdoid cells in AT/RT typically express EMA, vimentin, and SMA—an identification maker that can differentiate it from PNET and germ cell tumors (15,21). Our study observed EMA, SMA, and vimentin positivity in 66.7%, 70.4%, and 74.1% of cases, and a definitive diagnosis was based on the loss of INI1 expression.

Several studies have explored the risk factors for short survival and attempted to relate the clinical characteristics (sex, age at the time of diagnosis, the extent of resection, the effect of radiotherapy and chemotherapy) with the disease outcome (Table IV).

Influence of gross total tumor resection on event-free survival and overall survival was first mentioned by Hilden et al. in 2004 (16), and followed by many others. In 2005, Tekautz et al. reported a marginal advantage of GTR in 31 patients from St. Jude Cancer Research Center (33). Additionally, Chi et al. emphasized the benefit of the extent of resection on event-free survival and overall survival in a multi-institutional study of 20 patients (8). A recent 50-patient multi-institutional study pointed out that age, location, and presence of metastatic disease are not prognostic but suggested that GTR and high dose chemotherapy are favorable indicators (19).

Several single-center, multi-center, and registry studies have reported contradicting results regarding the effect of GTR on the outcome (2,10,35). Interestingly, one of the biggest multi-center series assessing 361 AT/RT cases does not report an increased survival duration with GTR (12). However, the patient cohort of that study was extracted from a national cancer database and extent of resection was unknown for most cases (64.0%)—probably why the influence of GTR was not considered.

In the present study, the extent of resection was a significant variable in univariate analysis but not in multivariate analysis. Interestingly, studies that report the extent of resection as a prognostic factor either give results for only univariate analysis or the effect of GTR is no longer significant when adjusted for other prognostic factors. Therefore, our results are in parallel with general literature.

The effect of radiotherapy on overall survival for patients older than three years is possibly more evident. For instance, Chen et al. report a correlation between failure-free survival and total irradiation dose, the time interval between surgery and radiotherapy initiation, thus indicating that deferring the initiation of radiation therapy had adverse effects on patient outcome (7). Previous publications have demonstrated the neurocognitive complications owing to whole-brain aggressive large-field radiation given to infants (27). Nonetheless, some authors encourage performing more focused conformal radiotherapy for young children with localized AT/RT based on the increase in overall and event-free survival rates with radiation therapy (12). Fischer-Valuck et al. demonstrated, through a large cohort of AT/RT patients, an increasing rate of radiation therapy given to younger children. Per the study, the hazards analysis of overall survival revealed hazard ratio of being diagnosed in between 2009-2012 is 0.58 when compared to the reference group (patients diagnosed between 2004-2008). Authors relate the survival benefit to increased utilization of radiotherapy in patients 0-2 years of age during the 2009-2012 period. With a cut-off point of 24 months for patient age at the time of diagnosis, we demonstrated that older children survived longer when compared to younger. The reason for choosing 24 months as the cut-off point was: First, because of the way the cohort was divided into two equal subgroups. Second, several studies in the literature compared survival differences in patients younger and older than two years of age. The finding regarding survival duration for older children in our study also conforms to general literature (12,35). As speculated by others, the unfavorable outcome

Table IV: Basic Clinical Characteristics and Their Impact on Survival According to Some Major Series in the Literature

Author	Number of patients	Sex	Age	Extent of resection	Tumor location	Metastatic disease	Complete remission	Radiation therapy
Chi et al., 2009 (8)	20	-	NS	Univariate	Univariate	NS	-	-
Dufour et al., 2012 (10)	58	-	Multivariate	NS	NS	Multivariate	-	-
von Hoff et al., 2011 (35)	56	-	Multivariate	Univariate	Univariate	Univariate	Univariate	NS
Lafay-Cousin et al., 2012 (19)	50	-	NS	Univariate	-	-	Univariate	NS
Buscariollo et al., 2012 (6)	144	NS	NS	NS	NS	Multivariate	-	Multivariate
Bartelheim et al., 2016 (2)	31	-	Univariate	NS	-	NS	Multivariate	Multivariate
Present study	27	Univariate	Univariate	Univariate	NS	NS	-	Multivariate

NS: *Not significant,* ***Univariate:*** *Variable significantly influences overall/progression free survival in univariate analysis,* ***Multivariate:*** *Variable significantly influences overall/progression free survival in multivariate analysis.*

in young patients might be partly because of limited use of radiotherapy—corroborated by the finding that when radiation therapy is given to patients under two years, their overall survival was similar to that of older children (12). Although the role of limited use of radiotherapy as a justification for the unfavorable outcome cannot be ignored, young age is associated with more aggressive behavior biologically.

Recently Johann et al. have identified three distinct molecular subgroups of AT/RT (17)—ATRT-TYR, ATRT-SHH, and ATRT-MYC. Their findings support that although all three AT/RT types are characterized by the prototypic loss of expression of *SMARCB1* or *SMARCB4*, the disease is heterogeneous with epigenetic differences. MRI characteristics of these three types, such as preferred tumor location, peritumoral edema, and contrast enhancement, have indeed been demonstrated; however, clinical differences in these subtypes are not apparent (23). This recent finding can probably explain the contradictions in risk factor identification for short survival and characteristics with favorable patient outcomes.

We herein assessed the overall survival of AT/RT cases related to various clinical features along with descriptive demographic and clinical information. Like several studies in the literature, our study has an analytical observational design (32), that diminishes its power. Another weakness in our study is the lack of progress-free survival or event-free survival rate; instead we could only give the overall survival rate. Unfortunately, insufficiency in collecting the data spanning over a considerable time resulted in this shortcoming. Despite the significant flaw, overall survival rates and survival rates for the subgroup of patients in our study compare well with the relevant literature. Unfortunately, there is no standardized treatment plan because of the rarity of AT/RT, and management strategies for this devastating disease are mainly individualized. This fact was reflected in our study as well wherein there was no established chemotherapy regimen. Therefore, it was not possible for us to evaluate the effects of different chemotherapeutics on survival.

CONCLUSION

AT/RT is a rare and dreadful brain tumor. Even with contemporary medicine, the survival rate is low, though promising studies are underway. A single-center randomized controlled study design is impractical owing to the rarity of the tumor. Therefore, larger trials explicitly designed for AT/RT that incorporates new tumor subtypes are needed to establish standard management strategies. Until that time, studies with rather small sample sizes, like ours, may contribute to the establishment of meta-analyses.

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