

# Atypical teratoid rhabdoid tumor in a lower middle-income country: Challenges to cure

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**Abstract.** Atypical teratoid rhabdoid tumor (ATRT) is a rare type of potentially fatal childhood brain tumor. The present study aimed to examine the overall survival (OS) and event-free survival (EFS) outcomes of pediatric patients with ATRT and to analyze the impact of different prognostic factors, including age, sex, tumor site and size, metastatic disease, the extent of resection, radiotherapy, and chemotherapy, on survival. The present study included 47 patients with ATRT treated at the Children's Cancer Hospital of Egypt (Cairo, Egypt) between July 2007 and December 2017. These patients were treated according to the Dana-Farber Cancer Institute protocol 02-294 for 51 weeks. Various prognostic factors, including age, sex, tumor size and initial metastatic status, exhibited no impact on the radiological response measured at 6 weeks and at the end of treatment.

The primary tumor site significantly affected the response to treatment at 6 weeks ( $P=0.008$ ). Toxicity-related mortality occurred in 29.8% of patients. The median duration of the treatment protocol was 66.9 weeks. The duration of treatment was in the present cohort was longer than the actual 51 weeks of the protocol due to prolonged supportive care of the included patients. Patients who encountered toxicity received reduced dose of chemotherapy in the subsequent cycles in the protocol. Age, initial metastatic status, tumor site and resection extent did not significantly affect the patient outcomes. Preoperative tumor size significantly affected the EFS ( $P=0.03$ ) and OS ( $P=0.04$ ). Radiotherapy administration significantly affected the OS ( $P<0.001$ ) and EFS ( $P<0.001$ ). The median EFS and OS of patients were 9.3 and 10.3 months, respectively. A total of 24 (51.1%) patients exhibited disease progression or recurrence. The progression sites were local ( $n=6$ ), metastatic ( $n=9$ ) or both local and metastatic ( $n=9$ ). The results of the present study demonstrated that the therapeutic regimen should be patient-adjusted to maintain the treatment intensity and avoid toxicity-related mortality. In lower middle-income countries, short and intensified induction followed by consolidation of treatment, either by single or tandem autologous stem cell transplant, is needed to avoid prolonged exposure to myelosuppression and toxicity-related mortality.

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*Abbreviations:* ATRT, atypical teratoid rhabdoid tumor; CNS, central nervous system; COG, Children's Oncology Group; CR, complete response; CTC, Common Toxicity Criteria; CSI, craniospinal irradiation; FLAIR, fluid-attenuated inversion recovery; GTR, gross total resection; INI1, integrase interactor 1; NTR, near-total resection; OS, overall survival; PD, progressive disease; SD, stable disease; SMARCB1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1; STR, subtotal resection

*Key words:* lower middle-income countries, challenges, cure, ATRT, outcome

## Introduction

Atypical teratoid rhabdoid tumor (ATRT) is a rare (1-2% of pediatric brain tumors) type of potentially fatal pediatric brain tumor (1). ATRT accounts for nearly half of the central nervous system (CNS) malignancies diagnosed during the first year of life (1). A total of 75% of patients with ATRT are <3 years old. Posterior fossa tumors predominate in infants, while supratentorial and spinal tumors are more common in children >3 years old. Metastatic disease occurs in ~30% of ATRT cases (1).

Rhabdoid tumors are characterized by mutations of the integrase interactor 1 (INI1) gene on chromosome 22. The absence of the INI1 protein, observed through immunohistochemical staining, is used to facilitate the diagnosis of this disease (2). Pathological features of ATRT could highlight specific molecular subgroups that need further confirmation through DNA methylation analysis (3). ATRT had four morphological categories: Rhabdoid, small-round-blue, epithelial and mesenchymal. The epithelial category is over-represented in ATRT-TYR, while the category small-round-blue category is over-represented in ATRT-SHH. The majority of ATRT-MYC was categorized as mesenchymal or rhabdoid (3).

ATRTs encompass three epigenetic subgroups with distinct genomic profiles and SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) genotypes: i) atrt-tyrosinase (TYR) tumors are more common in the infratentorial regions; ii) ATRT-MYC tumors are more common in the supratentorial regions; and iii) ATRT-sonic hedgehog (SHH) tumors are found in both infra- and supratentorial areas (4).

Currently, there is no standard chemotherapeutic regimen for the treatment of patients with ATRT. Alkylating agents, high-dose methotrexate or high-dose chemotherapy with stem cell transplantation are the most recommended regimens of treatment (5). A multimodal treatment strategy that involved maximal safe resection, standard dose chemotherapy, radiation therapy and high-dose chemotherapy improved the survival rates of patients, but caused notable toxicity due to the young age of the patients who could not tolerate this aggressive approach (1).

The present study aimed to investigate the outcome of pediatric ATRT at the Children's Cancer Hospital of Egypt (Cairo, Egypt). Different prognostic factors, such as age, metastatic phenotype (M+), primary tumor site, tumor size, extent of resection [gross total resection (GTR) vs. subtotal resection (STR)], field of radiotherapy, chemotherapy dose intensity (full vs. reduced dose) and remission status after 6 weeks of induction, were analyzed and their association with patient survival was examined.

## Materials and methods

**Patient population.** The present retrospective study included 47 patients with ATRT treated at the Children's Cancer Hospital of Egypt (Cairo, Egypt) between July 2007 and December 2017. Patients were treated according to the Dana-Farber Cancer Institute (DFCI) protocol 02-294 (6). All patients diagnosed with ATRT at  $\leq 18$  years of age with available pathological specimen and complete data in their electronic files were included. Patients who received chemotherapy or radiotherapy outside the hospital or their data were missing from the electronic files were excluded.

Data were retrieved from the electronic files of patients after ethics approval was obtained from the Institutional Review Board of the Children's Cancer Hospital of Egypt (approval no. 33/2019; Cairo, Egypt). The requirement for written patient consent was waived due to the retrospective nature of the present study. The patients or legal guardians were contacted for any information that was unavailable in the patient files. Oral consent was obtained from the parents

or legal guardians of the patients over the phone due to their inability to travel to the hospital. All patient data were anonymized to protect their privacy and confidentiality.

The following data were retrieved from the patient files: Age, sex, initial tumor size, tumor site, the presence of metastatic disease, response to treatment, types and grades of different toxicities according to Common Toxicity Criteria (CTC) version V (7), date of progression or disease recurrence, date of the end of treatment, and date of death. The extent of surgical resection was classified into GTR (no evidence of residual tumor), near-total resection (NTR;  $\leq 1.5$  cm<sup>2</sup> residual tumor), STR ( $\geq 1.5$  cm<sup>2</sup> residual tumor) and debulking surgery or biopsy (8). All patients were pathologically diagnosed with grade IV ATRT with a loss of INI1 expression according to the World Health Organization guidelines (9). Patient responses were assessed twice, once during pre-irradiation at 6 weeks and once at the end of treatment. The radiological response was assessed according to the Response Assessment in Neuro-Oncology criteria (10). Complete response (CR) was defined by the following criteria: i) Complete disappearance of all enhancing measurable and non-measurable disease sustained for  $\geq 4$  weeks; ii) no new lesions; iii) stable or improved non-enhancing T2/fluid-attenuated inversion recovery (FLAIR) lesions; and iv) stable or improved clinical condition without any medical support as assessed by the primary physician. Partial response (PR) was achieved if the following criteria were met: i) A total of  $\geq 50\%$  decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for  $\geq 4$  weeks; ii) no progression of non-measurable disease; iii) no new lesions; iv) stable or improved non-enhancing T2/FLAIR lesions on the same or a lower dose of corticosteroids; and v) clinically stable or improved condition. Stable disease (SD) was achieved if the following criteria were met: i) Patient did not qualify for CR, PR or progressive disease (PD); and ii) stable non-enhancing T2/FLAIR lesions were observed on the same or a lower dose of corticosteroids compared with the baseline scan. PD was defined using the following criteria: i) A total of  $\geq 25\%$  increase in the sum of products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response on stable or increasing doses of corticosteroids; and ii) a significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids. Measurable disease was defined by dimensional contrast-enhancing lesions with clearly defined margins, with two perpendicular diameters  $\geq 10$  mm, visible on  $\geq 2$  axial slices. Non-measurable lesions were those lesions without enhancement and assessed by their flair uptake.

**Treatment details.** All patients were subjected to maximal safe resection. The extent of resection was assessed by MRI brain and intraoperative neurosurgical assessment to decide the resection of the tumor without jeopardizing vital structure. Two patients had no available data regarding the location of the surgery performed, and the families were unable to state the hospitals where surgeries were carried out. The treatment protocol lasted 51 weeks and included the following phases: Induction, maintenance and continuation therapy (using either doxorubicin or actinomycin therapy). This regimen is similar

to that applied by the DFCI with which our center had collaboration facilitating the adoption of this protocol (6).

The induction phase consisted of 14 weeks of chemotherapy. For the first 6 weeks, chemotherapy was administered pre-irradiation, the following 6 weeks chemotherapy was administered during the radiation therapy, and the last 2 weeks chemotherapy was administered post-radiation with an interval of 3 weeks between every cycle of chemotherapy. After week 6, patients with residual disease would undergo second-look surgery.

Age-adapted radiotherapy was implemented, whereby patients <3 years old received focal irradiation regardless of their metastatic status. Only M+ patients >3 years old received craniospinal irradiation (CSI). The dose for focal radiotherapy ranged between 4,800 and 5,900 cGy given for 6 weeks (5 days/week) with total of 31 sessions. Younger patients were treated with a lower dose. Regarding the craniospinal dose, 2 patients received 2,340 cGy CSI with boost radiation of the tumor bed up to 5,040 cGy, while 2 patients received a reduced dose of 3,600 cGy CSI with boost radiation of the tumor bed ≤5,400 cGy.

The maintenance chemotherapy phase lasted 23 weeks. The continuation therapy consisted of 3 weeks of chemotherapy and was performed with or without doxorubicin depending on the radiation field received. Patients receiving CSI received non-doxorubicin continuation therapy to minimize further cardiotoxicity. The details of the full treatment protocol are presented in Fig. S1. The type and grade of toxicities were collected and graded according to the CTC version V. Patients who encountered grade 3-4 toxicity were treated with a chemotherapy dose that was reduced by 25% in subsequent cycles regardless of the phase of therapy.

**Statistical analysis.** All statistical analyses were conducted using SPSS (version 23; IBM Corp.). The study endpoints included overall survival (OS) and event-free survival (EFS). OS was calculated as the time from registration until death or last contact with the patient, while EFS was calculated as the time until recurrence, progression, death or last contact with the patient. Survival analyses were performed using the Kaplan-Meier estimator function and standard errors were calculated using Greenwood's formula. The two-sided log-rank test was used to compare survival curves of potential prognostic factors. Median follow-up was determined using the reverse Kaplan-Meier method. Enumeration data are presented as n (%) and were analyzed with  $\chi^2$  or Fisher's exact tests.  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Patient characteristics.** The present study retrospectively included 47 patients with ATRT (Table I). The median age of patients was 2.4 years (range, 0.5-16.9 years). A total of 30 patients (63.8%) were <3 years old, while 17 patients (36.2%) were ≥3 years old. The male-to-female ratio of the patient cohort was 1.14:1. A total of 26 patients (55.3%) had supratentorial tumors, 18 patients (38.3%) had infratentorial tumors, three patients (6.4%) had spinal ATRT and 14/47 patients (29.8%) had metastatic tumors. Among the

Table I. Characteristics of the 47 patients with atypical teratoid rhabdoid tumor in the present study.

Patient characteristic	n (%)
Sex	
Male	25 (53.2)
Female	22 (46.8)
Age, years	
<3	30 (63.8)
≥3	17 (36.2)
Primary tumor site	
Supratentorial	26 (55.3)
Infratentorial	18 (38.3)
Spinal cord	3 (6.4)
Maximum tumor diameter, cm	
<5	22 (46.8)
≥5	23 (48.9)
Unknown	2 (4.3)
Extent of tumor resection	
Gross total resection/near-total resection	22 (46.8)
Subtotal resection	8 (17.0)
Debulking or biopsy	16 (34.0)
Unknown	1 (2.1)
Metastasis	
No	33 (70.2)
Yes	14 (29.8)
Chemotherapy	
No	2 (4.3)
Yes	45 (95.7)
Full dose	40 (88.9)
Reduced dose	5 (11.1)
Radiotherapy	
No	18 (38.3)
Yes	29 (61.7)
Focal	23 (79.3)
Craniospinal	4 (13.8)
Unknown	2 (6.9)

14 patients with metastatic tumors, nine patients (64.3%) were <3 years old, while 5 patients (35.7%) were ≥3 years old. The median maximum tumor dimension was 5.2 cm (range, 1.6-14.5 cm). Among all patients, 22/47 patients (46.8%) had a preoperative maximum tumor diameter <5 cm. In comparison, 23/47 patients (48.9%) had a tumor diameter ≥5 cm, whilst two patient files did not contain available initial imaging data. GTR/NTR was achieved in 22/47 patients (46.8%), STR was achieved in 8/47 patients (17.0%), and 16/47 patients (34.0%) underwent a biopsy only. A single (2.1%) patient was not assessed postoperatively but no indication regarding the reasoning was found in the patient's medical file. No patients underwent second-look surgery.

A total of 40/45 patients (88.9%) received full-dose chemotherapy, while 5/45 patients (11.1%) received chemotherapy

Table II. Association between different prognostic factors and response of patients with atypical teratoid rhabdoid tumor after 6 weeks of treatment.

Prognostic factor	No.	Complete response, stable disease or partial response, n (%)	Disease progression or recurrence, n (%)	P-value
Age, years				0.185
<3	19	17 (89.5)	2 (10.5)	
≥3	14	10 (71.4)	4 (28.6)	
Sex				0.615
Male	19	15 (78.9)	4 (21.1)	
Female	14	12 (85.7)	2 (14.3)	
Primary tumor site				0.008
Supratentorial	18	16 (88.9)	2 (11.1)	
Infratentorial	13	11 (84.6)	2 (15.4)	
Spinal cord	2	0 (0.0)	2 (100.0)	
Maximum tumor diameter, cm				0.289
<5	18	15 (83.3)	3 (16.7)	
≥5	15	11 (73.3)	4 (26.7)	
Location surgery was performed				0.498
Children's Cancer Hospital of Egypt	31	25 (80.6)	6 (19.4)	
Other institutions	2	2 (100.0)	0 (0.0)	
Extent of tumor resection				0.616
Gross total resection or near-total resection	16	14 (87.5)	2 (12.5)	
Subtotal resection	6	5 (83.3)	1 (16.7)	
Debulking or biopsy	11	8 (72.7)	3 (27.3)	
Metastasis				0.717
No	24	20 (83.3)	4 (16.7)	
Yes	9	7 (77.8)	2 (22.2)	

$\chi^2$ -test was used for statistical analysis.

with dose reduction due to chemotherapy toxicity. Two patients did not receive chemotherapy due to patients' guardian refusal. A total of 11/45 patients (24.4%) reached the end of the treatment protocol and the rest died at different phases of treatment, whilst 33 patients (73.3%) completed the pre-irradiation phase of the treatment and were evaluated at week 6. At week 6, 9/33 patients (27.3%) achieved CR, 15/33 patients (45.5%) achieved PR, 3/33 patients (9.1%) had SD, 4/33 patients (12.1%) had PD and 2/33 patients (6.1%) did not undergo imaging.

A total of 29/47 patients (61.7%) received radiation therapy. A total of 23/29 patients (79.3%) received focal radiation, whilst 4/29 patients (13.8%) received CSI. The radiotherapy details were missing for two patients. Not all patients received radiation therapy either due to poor general condition or due to PD before radiotherapy. The median duration of the treatment protocol was 66.9 weeks (range, 60.1-84.4 weeks). The long duration of therapy compared to the number of weeks of the protocol is related to the encountered toxicity with prolonged supportive care.

**Prognostic factors.** There was no significant impact of the following prognostic factors on the response at week 6: Age (P=0.185), sex (P=0.615), tumor size (P=0.289), surgery

(P=0.498), extent of resection (P=0.616) and initial metastatic status (P=0.717) (Table II). The primary tumor site (supratentorial vs. infratentorial vs. spinal) significantly affected the response at week 6 (P=0.008). After excluding the 2 cases of spinal ATRT, there was no significant difference between the supratentorial and infratentorial sites (P=0.6). Various prognostic factors such as age, sex, tumor size, extent of resection and metastatic status had no significant impact on the response at the end of treatment. The median EFS for patients <3 years old was 9.3 months (95% CI, 2.3-16.4 months), while it was 8.1 months (95% CI, 0.0-16.4 months) for patients ≥3 years old. The 1-year EFS and OS for patients <3 years old were 33.3% (95% CI, 16.4-50.2) and 36.7% (95% CI, 19.5-53.9), respectively, and these were 35.3% (95% CI, 12.6-58.0) and 41.2% (95% CI, 17.9-64.5), respectively, for patients ≥3 years old (EFS, P=0.75; Fig. 1; OS, P=0.56; Fig. 2). The 2-year OS was 20.0% (95% CI, 5.7-34.3) for patients <3 years old, compared with 29.4% (95% CI, 7.6-51.2), respectively, for patients ≥3 years old.

Patient sex (EFS, P=0.42; Fig. 3; OS, P=0.56; Fig. 4), primary tumor site (EFS, P=0.35; Fig. 5; OS, P=0.44; Fig. 6), metastatic disease (EFS, P=0.21; Fig. 7; OS, P=0.25; Fig. 8) and extent of resection (EFS, P=0.58; Fig. 9; OS, P=0.56; Fig. 10) did not have a significant impact on the treatment outcome.

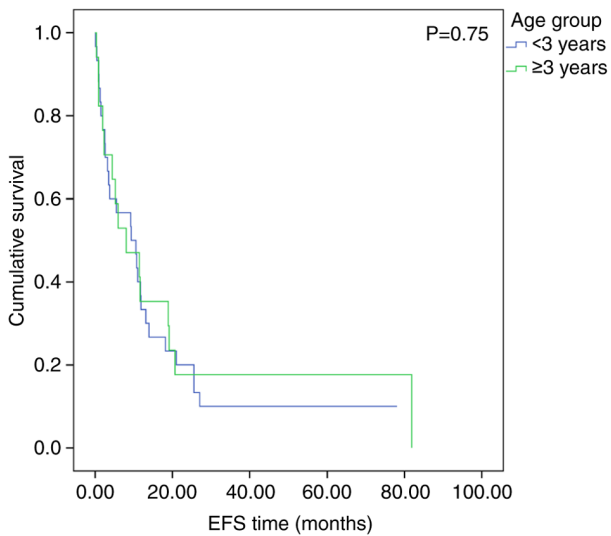


Figure 1. Association between age and EFS in patients with atypical teratoid rhabdoid tumor. EFS, event-free survival.

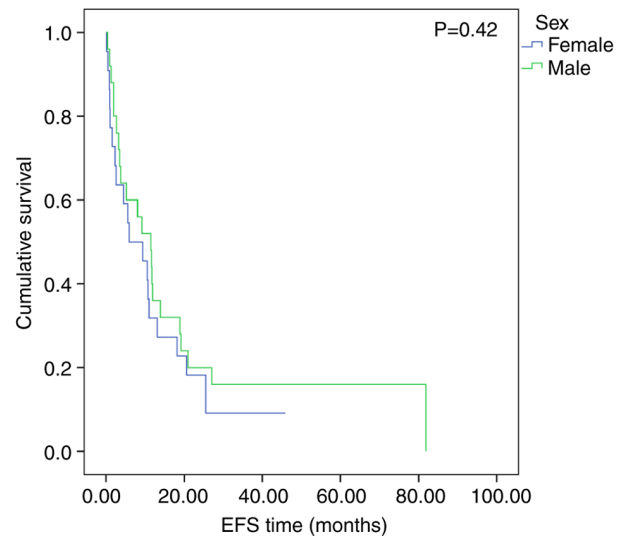


Figure 3. Association between sex and EFS in patients with atypical teratoid rhabdoid tumor. EFS, event-free survival.

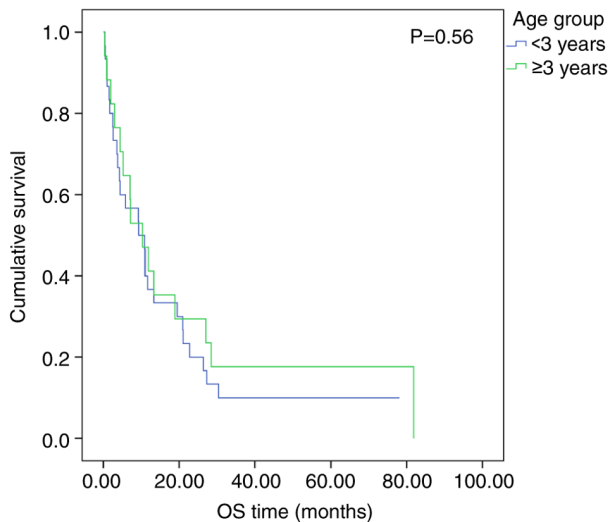


Figure 2. Association between age and OS in patients with atypical teratoid rhabdoid tumor. OS, overall survival.

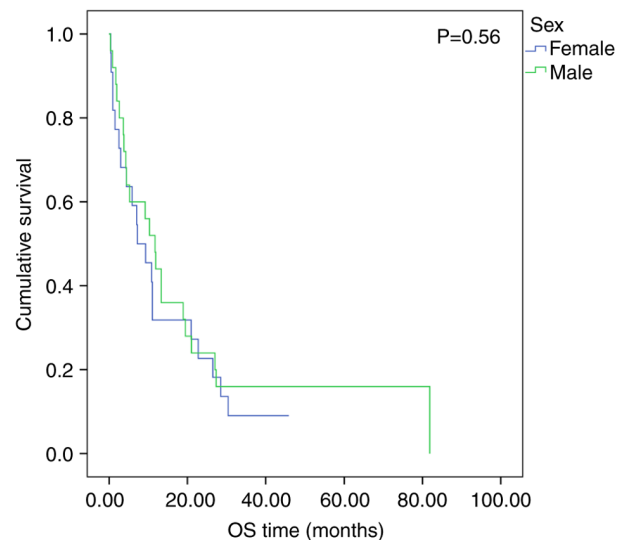


Figure 4. Association between sex and OS in patients with atypical teratoid rhabdoid tumor. OS, overall survival.

The median EFS and OS for patients <3 years old with metastatic disease were 9.4 months (95% CI, 6.8-12.8 months) and 7.7 months (95% CI, 3.6-15.8 months), respectively, and those for patients ≥3 years old were 10.6 months (95% CI, 8.1-13.2 months) and 8.3 months (95% CI, 2.1-14.5 months), respectively (EFS,  $P=0.498$ ; OS,  $P=0.993$ ; data not shown).

Preoperative tumor size significantly affected both EFS and OS. The median EFS for tumors <5 cm was 11.7 months (95% CI, 3.2-20.3 months), while the median EFS for tumors ≥5 cm was 6.0 months (95% CI, 0.3-11.6 months). The 1-year EFS for patients with tumor size <5 or ≥5 cm was 45.5% (95% CI, 24.7-66.3) and 21.7% (95% CI, 4.8-38.6), respectively ( $P=0.03$ ; Fig. 11).

The median OS for tumors <5 or ≥5 cm was 11.9 months (95% CI, 2.8-21.0 months) and 7.2 months (95% CI, 1.0-13.4 months), respectively. The 1-year and 2-year OS for patients with tumors <5 cm was 50.0% (95% CI, 29.0-71.0) and

36.4% (95% CI, 16.2-56.6), respectively, compared with 26.1% (95% CI, 8.1-44.1) and 8.7% (95% CI, 0.0-20.3), respectively, for patients with tumors ≥5 cm ( $P=0.04$ ; Fig. 12).

Chemotherapy dose reduction did not have a significant negative impact on the outcome of treatment. The median EFS for patients who received a full dose of chemotherapy was 8.1 months (95% CI, 2.1-14.0 months), while the median EFS for patients who received a reduced dose was 20.7 months (95% CI, 6.3-35.1 months). The 1-year EFS for patients who received the full or the reduced dose was 30.0% (95% CI, 15.9-44.1) and 80.0% (95% CI, 44.9-100.0), respectively, which had clinical significance, although no statistical significance was observed ( $P=0.08$ ; Fig. 13).

The median OS for patients who received a full dose of chemotherapy was 9.2 months (95% CI, 4.1-14.3 months), while the median OS for patients who received a reduced dose was 28.5 months (95% CI, 9.2-47.7 months). The 1- and

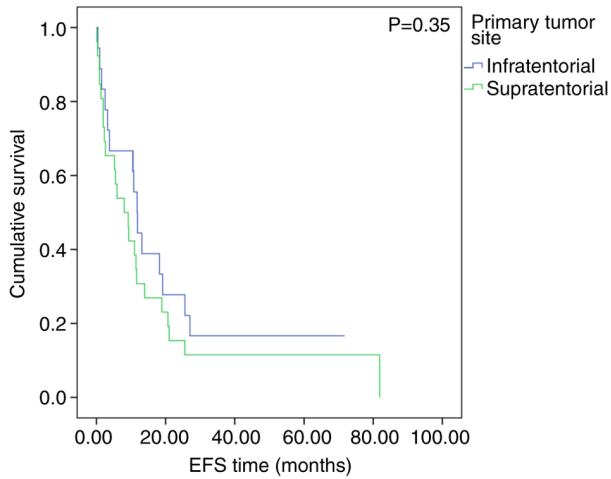


Figure 5. Association between primary tumor site and EFS in patients with atypical teratoid rhabdoid tumor. EFS, event-free survival.

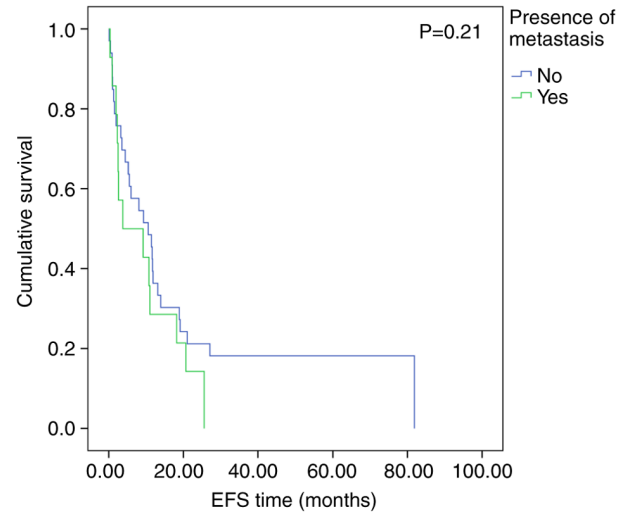


Figure 7. Association between initial metastatic status and EFS in patients with atypical teratoid rhabdoid tumor. EFS, event-free survival.

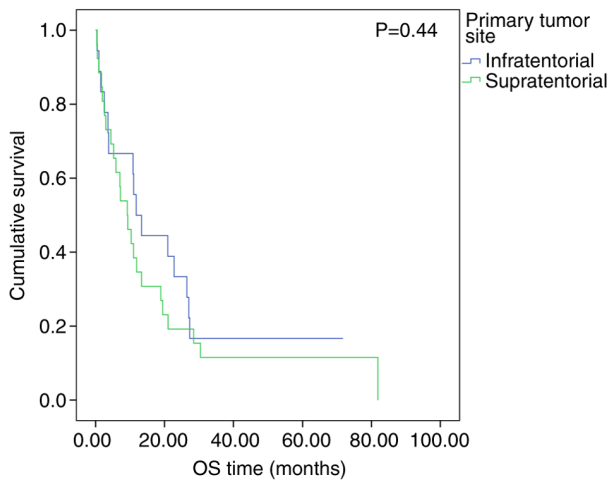


Figure 6. Association between primary tumor site and OS in patients with atypical teratoid rhabdoid tumor. OS, overall survival.

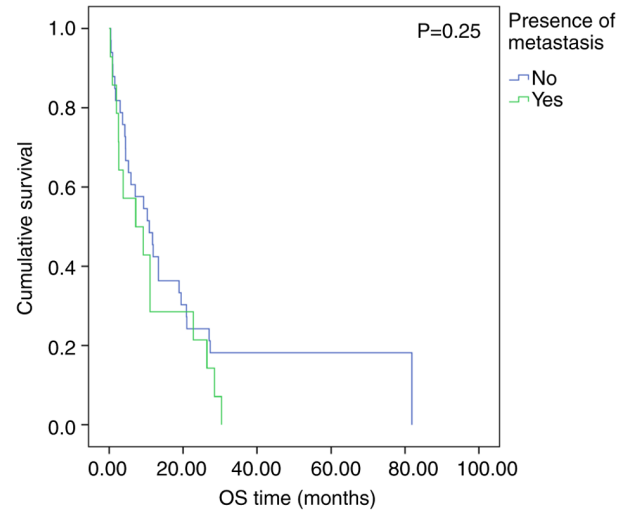


Figure 8. Association between initial metastatic status and OS in patients with atypical teratoid rhabdoid tumor. OS, overall survival.

2-year OS was 35.0% (95% CI, 20.3-49.7) and 20.0% (95% CI, 7.7-32.3), respectively, for patients who received the full dose, compared with 80.0% (95% CI, 44.9-100.0) and 60.0% (95% CI, 17.1-100.0), respectively, for patients who received the reduced dose ( $P=0.06$ ; Fig. 14).

Radiotherapy administration significantly impacted the treatment outcome. The median EFS and OS for patients who received radiotherapy were 13.9 months (95% CI, 2.8-25.0 months) and 19.5 months (95% CI, 6.1-32.8 months), respectively. The median EFS and OS for patients who did not receive radiotherapy were 1.5 months (95% CI, 0.6-2.5 months) and 2.0 months (95% CI, 0.3-3.6 months), respectively. The 1-year EFS for patients who received radiotherapy and those who did not was 55.2% (95% CI, 37.2-73.2) and 0.0%, respectively ( $P<0.001$ ; Fig. 15). The 1- and 2-year OS were 62.1% (95% CI, 44.5-79.7) and 37.9% (95% CI, 20.3-55.5) for patients who received radiotherapy, vs. 0% for those who did not receive radiotherapy ( $P<0.001$ ; Fig. 16). The radiotherapy field had no statistically significant effect on the treatment outcome (EFS,  $P=0.74$ ; Fig. 17; OS,  $P=0.71$ ; Fig. 18).

**Treatment-related toxicity.** A total of 43/47 patients (91.5%) patients reported  $\geq 1$  treatment-related toxicity. These toxicities were reported in all 40 patients who received full dose chemotherapy and in 3/5 patients who received a reduced dose of chemotherapy. All patients who received focal or CSI radiotherapy developed treatment-related toxicity. A total of 3/47 patients (6.4%) patients had no available data about their toxicity profile, whilst one patient (2.1%) did not develop any treatment-related toxicity. Blood cultures were performed for 39/47 patients (83.0%) patients due to shortage of blood culture bottles in the hospital. The majority of the bacterial species recovered from these cultures were gram-negative (33/39; 84.6%). The most commonly isolated bacteria were *Escherichia coli* ( $n=18$ ), *Klebsiella pneumoniae* ( $n=8$ ), *Pseudomonas aeruginosa* ( $n=4$ ) and *Acinetobacter baumannii* ( $n=3$ ). Gram-positive bacteria were isolated in 6/39 patients (15.4%), and the most commonly isolated gram-positive bacterium was *Staphylococcus aureus*. Central line-associated

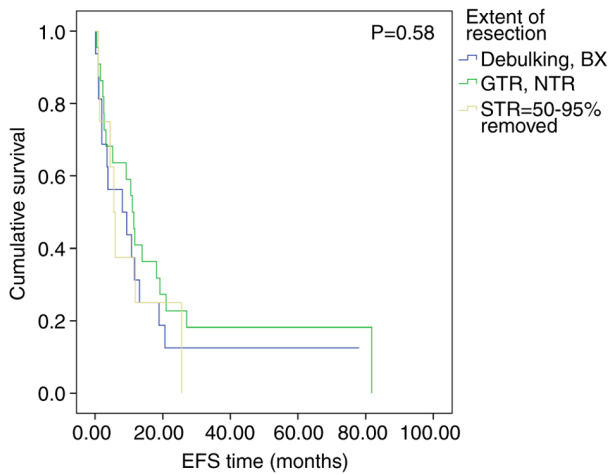


Figure 9. Association between the extent of tumor resection and EFS in patients with atypical teratoid rhabdoid tumor. BX, biopsy; EFS, event-free survival; GTR, gross total resection; NTR, near-total resection; STR, subtotal resection.

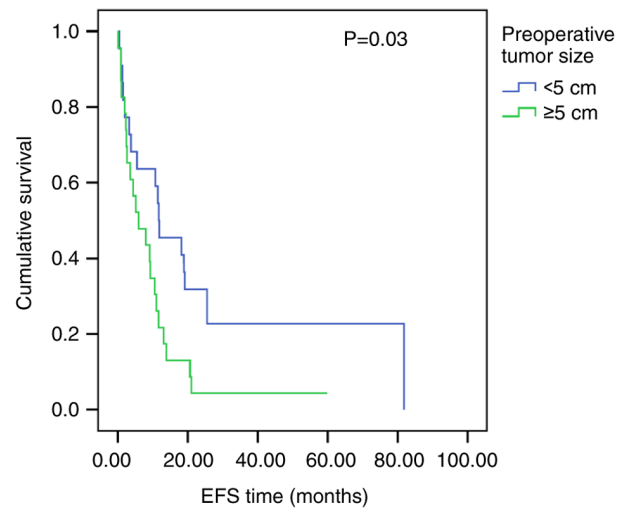


Figure 11. Association between preoperative tumor size and EFS in patients with atypical teratoid rhabdoid tumor. EFS, event-free survival.

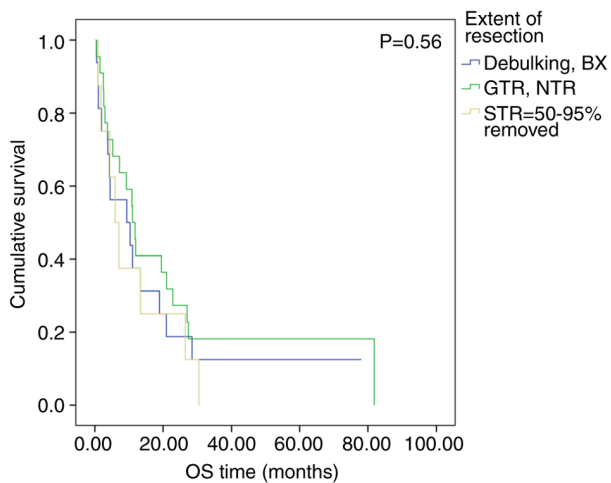


Figure 10. Association between the extent of tumor resection and OS in patients with atypical teratoid rhabdoid tumor. BX, biopsy; GTR, gross total resection; NTR, near-total resection; STR, subtotal resection. OS, overall survival.

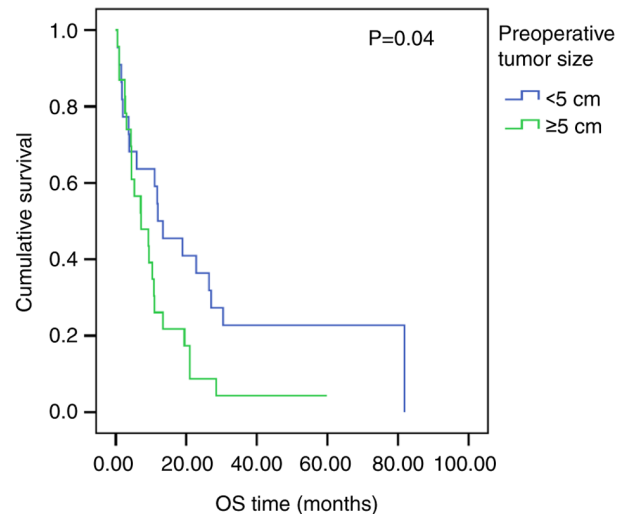


Figure 12. Association between preoperative tumor size and OS in patients with atypical teratoid rhabdoid tumor. OS, overall survival.

bloodstream gram-negative infections were reported in 12/33 patients (36.4%) as follows: *Escherichia coli* (n=5), *Klebsiella pneumoniae* (n=4), *Pseudomonas aeruginosa* (n=2) and *Acinetobacter baumannii* (n=1).

**Survival outcome.** The median follow-up period of the patients was 71.7 months. The median EFS and OS for all patients were 9.3 months (95% CI, 2.9-15.8 months) and 10.3 months (95% CI, 0.4-81.4 months), respectively, with an estimated 1-year and 2-year EFS of 34.0% (95% CI, 20.5-47.5) and 19.1% (95% CI, 7.8-30.2), respectively (Fig. 19). The 1-, 2- and 3-year OS of the patient cohort was 38.3% (95% CI, 24.4-52.2), 23.4% (95% CI, 11.2-35.6) and 12.8% (95% CI, 3.2-22.4), respectively (Fig. 20). A total of 24/47 patients (51.1%) exhibited disease progression or recurrence. The progression site was either local (n=6), metastatic (n=9) or both local and metastatic (n=9).

**Causes of mortality.** Toxicity-related mortality occurred in 14/47 patients (29.8%). A total of 8/14 patients (57.1%) died from gram-negative septicemia due to *Escherichia coli* (n=2), *Klebsiella pneumoniae* (n=5) or *Pseudomonas aeruginosa* (n=1) infections. A total of 5/14 patients (35.7%) died from severe pneumonia, whilst 1 (7.1%) patient developed grade V platinum toxicity with electrolyte disturbance, which led to acute renal failure.

## Discussion

ATRT is a rare disease, and clinical trials investigating the treatment modalities are largely non-randomized, single-arm, collaborative, multi-centric studies from Europe and North America. Real-world data on this rare disease are scarce, especially from low middle-income countries (11). The present study reported the treatment outcomes of patients with ATRT from a large pediatric cancer center in Egypt (Children's

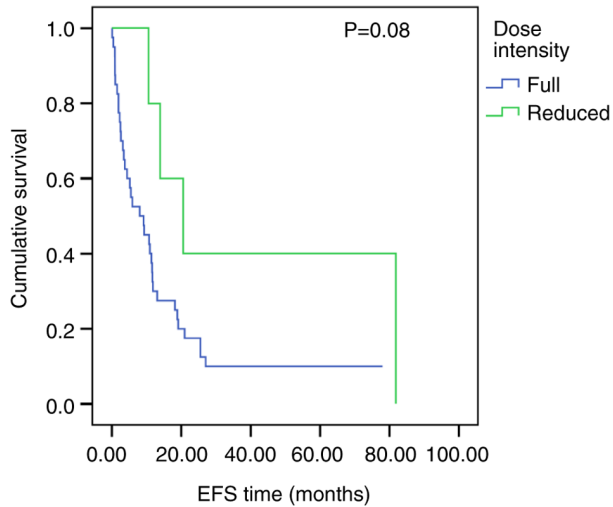


Figure 13. Association between chemotherapy dose intensity and EFS in patients with atypical teratoid rhabdoid tumor. EFS, event-free survival.

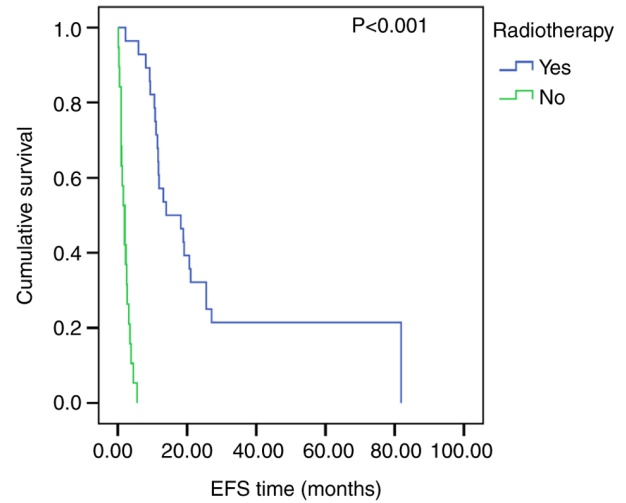


Figure 15. Association between radiotherapy administration and EFS in patients with atypical teratoid rhabdoid tumor. EFS, event-free survival.

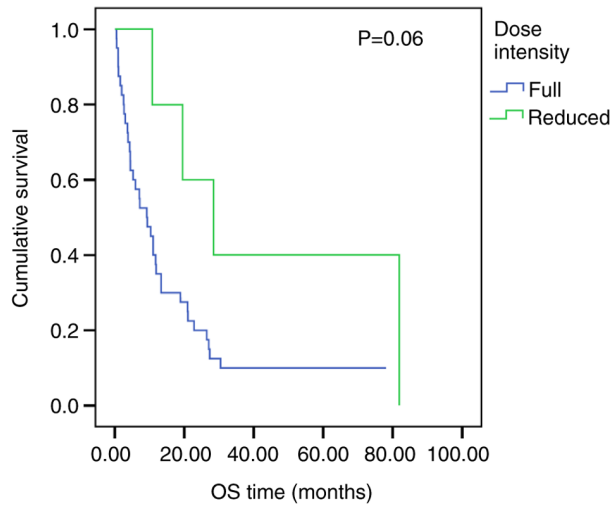


Figure 14. Association between chemotherapy dose intensity and OS in patients with atypical teratoid rhabdoid tumor. OS, overall survival.

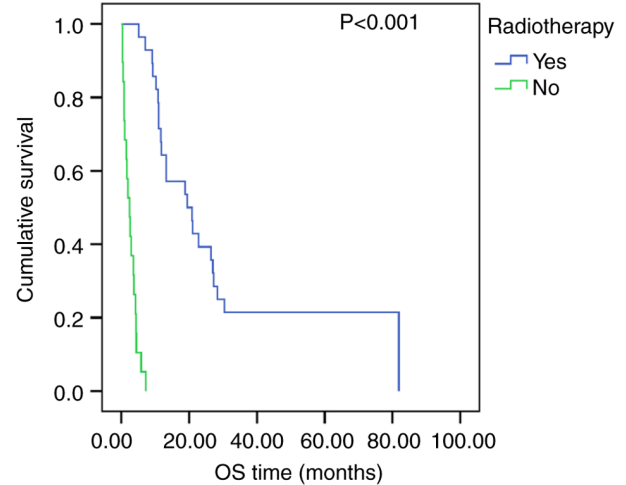


Figure 16. Association between radiotherapy administration and OS in patients with atypical teratoid rhabdoid tumor. OS, overall survival.

Cancer Hospital of Egypt, Cairo), using a unified treatment protocol with an intensive multimodality approach of maximal safe resection, systemic and intrathecal chemotherapy, and age-adjusted radiation therapy.

In the present study, 30 (63.8%) patients were <math>< 3</math> years old at the time of presentation. The median age of the patients was 28.8 months (2.4 years), which was consistent with a number of previous reports, including the North American ATRT registry (24 months) (11), the European Rhabdoid Registry (EU-RHAB; 29.5 months) (12) and the DFCI cohort (26 months) (6). The percentage of patients <math>< 3</math> years old was higher in the Children's Oncology Group (COG) ACNS0333 study cohort (83%) (13).

The present study demonstrated that patient age did not have a significant impact on the treatment outcome. This finding is in accordance with the study published by Upadhyaya *et al* (14) who analyzed 74 patients newly diagnosed with ATRT, who were treated either in the SJYC07 trial (age, <math>< 3</math> years;  $n=52$ ) or SJMB03 trial (age, 3-21 years;

$n=22$ ). In the SJYC07 trial, patients with non-metastatic (M0) disease ( $n=34$ ) had a 5-year progression-free survival (PFS) of  $39.1 \pm 11.5\%$  and OS of  $51.8 \pm 12.0\%$ , whereas the 5-year PFS and OS for patients with M+ disease ( $n=18$ ) were both 0.0% (14). Additionally, survival did not differ by age at diagnosis, sex, primary tumor site and extent of resection for those with intermediate risk disease, which is consistent with the results of the present study (14). According to the SJMB03 clinical trial data, children with average risk (M0 disease and  $< 1.5 \text{ cm}^2$  residual tumor;  $n=11$ ) had a 5-year PFS and OS of  $72.7 \pm 12.7$  and  $81.8 \pm 11\%$ , respectively, whereas those with high-risk disease (M+ or  $> 1.5 \text{ cm}$  residual) ( $n=11$ ) had a 5-year PFS and OS of  $18.2 \pm 9.5\%$  (14). Additionally, Chi *et al* (6) reported that age did not have an impact on the survival outcome (6). By contrast, the EU-RHAB study reported that age was the most important prognostic factor of survival with a 5-year OS of  $16.7 \pm 5.7\%$  for patients <math>< 12</math> months old at diagnosis vs.  $45.3 \pm 6\%$  for those  $\geq 12$  months old (12).



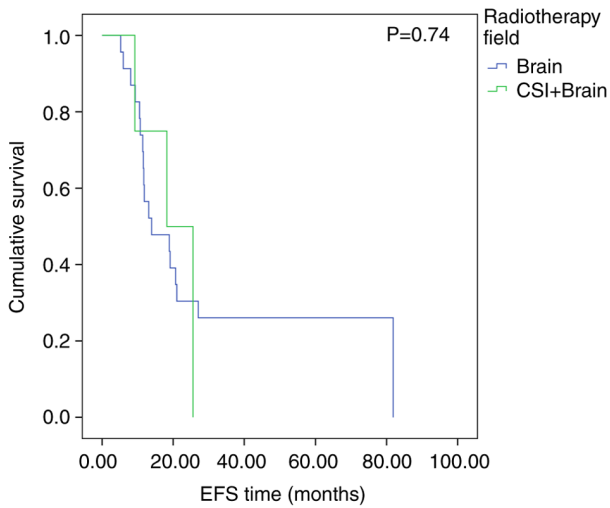


Figure 17. Association between field of radiotherapy and EFS in patients with atypical teratoid rhabdoid tumor. CSI, craniospinal irradiation. EFS, event-free survival.

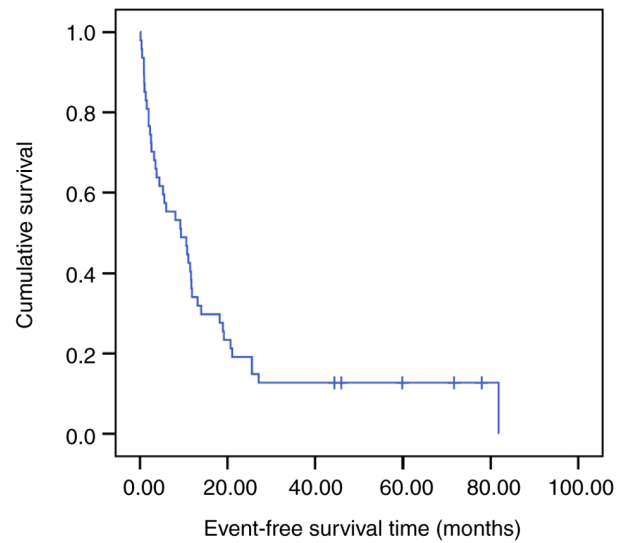


Figure 19. EFS of all patients with atypical teratoid rhabdoid tumor in the present study. EFS, event-free survival.

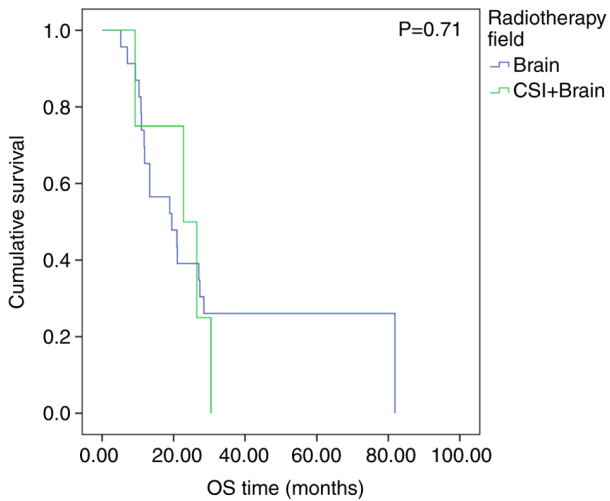


Figure 18. Association between field of radiotherapy and OS in patients with atypical teratoid rhabdoid tumor. CSI, craniospinal irradiation; OS, overall survival.

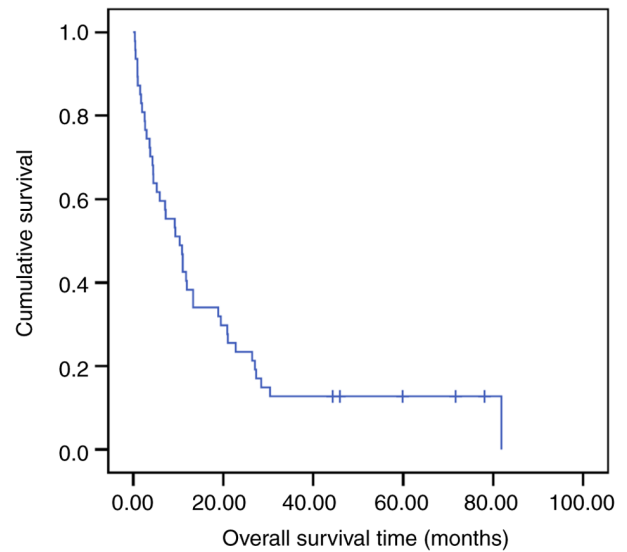


Figure 20. OS of all patients with atypical teratoid rhabdoid tumor in the present study. OS, overall survival.

In the present study, the primary tumor site did not have a significant impact on the survival of patients. This result differed from that reported by Chi *et al* who indicated that the tumor location markedly affected OS. The median OS for patients with supratentorial tumors was 24 months, whereas the median OS was not reached for patients with posterior fossa tumors (P=0.04) (6). The absence of an association between the primary tumor site and the outcome in the present study was consistent with the COG ACNS0333 results and the St. Jude trials data (13,14).

We hypothesized that Egyptian patients with ATRT may be diagnosed later compared with cases in high-income countries due to the long waiting lists and poor parental awareness about this disease, which leads to more prevalent metastatic disease at the time of presentation. However, in the present study cohort, 70.2% of patients were M0, similar to other published data, including the DFCI (70%), EU-RHAB (70.0%) and ACNS0333 (63.0%) studies (6,12,13).

The present results demonstrated that the presence of metastasis did not significantly impact the treatment outcome. This result was similar to previous studies published from the DFCI and ACNS0333 (6,13). The lack of association may be partially attributed to unpowered, unadjusted subgroup analysis. By contrast, the EU-RHAB study reported a superior survival for 100 M0 cases with a 5-year OS of 43.0% compared with 16.9% for M+ patients (P<0.0001) (12).

The negative impact of metastatic disease on survival was demonstrated in the SJYC07 trial, where patients with M0 disease had a 5-year PFS of 39.1±11.5% and OS of 51.8±12.0%, compared with 0.0% for both PFS and OS for those with M+ disease (P<0.001) (14).

In the present cohort, large tumor diameters (≥5 cm) were associated with significantly decreased EFS (P=0.03) and OS (P=0.04). To the best of our knowledge, this factor is a vital

prognostic variable that has not currently been reported in the literature.

The extent of tumor resection did not significantly affect the survival of patients in the present study. This finding is supported by a previously published individual patient pooled meta-analysis of 332 cases with ATRT and results obtained from the EU-RHAB study (12,15). The DFCI study reported contradictory results compared with the present study data; GTR/NTR was associated with a 2-year OS of 91% (6). Furthermore, the Canadian Pediatric Brain Tumor Consortium reported that patients with GTR had a 2-year OS of 60.0±12.6% compared with 21.7±8.5% for those who underwent alternative treatment to GTR (P=0.03) (16).

In the present cohort, patients who received radiotherapy showed a significantly superior median EFS (P<0.001) and OS (P<0.001) compared with those who did not receive radiotherapy (13.9 vs. 1.5 months and 19.5 vs. 2.0 months, respectively). Similarly, Schrey *et al* (15) reported higher EFS and OS rates for patients receiving irradiation, in addition to improved radiological response at the end of treatment (15).

The median EFS and OS for all patients included in the present study were 9.3 months (95% CI, 2.9-15.8 months) and 10.3 months (95% CI, 0.4-81.4 months), respectively, which was lower than those reported in a previous report with a 4-year OS of 50% (6). A total of 24 (89.4%) patients either exhibited disease progression or recurrence. The progression sites were local, metastatic or both local and metastatic. In the SJYC07 trial, the pattern of failure for IR patients (n=23) was local (n=9), distant (n=8) or combined (n=6) (14).

The present study reported an inferior treatment outcome compared with a previous study by Chi *et al* (6), due to higher mortality rate in the present study (29.8 vs. 5%). This could potentially be attributed to the majority of the patients in the present study living in low socioeconomic areas. These patients were more likely to be infected by gram-negative bacteria, which caused severe septicemia during the repeated and prolonged period of myelosuppression. Furthermore, poor patient hygiene and made patients susceptible to severe pneumonia, especially during the immunosuppression period. Certain patients could not maintain a high chemotherapy dose intensity due to a prolonged supportive period, as highlighted by the high median therapy duration reported in the present study. Therefore, administering a patient-specific chemotherapy dose intensity could decrease infectious complications and maintain dose intensity without treatment interruption.

Furthermore, a short, intensified induction followed by intensified consolidation, either single as Head Start or tandem transplant, as reported in the COG ACNS0333 study, may enhance CNS prophylaxis using high-dose methotrexate. The long treatment protocol duration (51 weeks) may increase the probability of community-acquired infections observed in the patients of the present study who live in low socioeconomic areas, which can contribute to higher rates of toxicity-related mortality.

The limitations of the present study included its retrospective nature and incomplete data on detailed toxicities and chemotherapy protocol modifications. Furthermore, the frequency of neurocognitive deficits was not measured. The present study also did not investigate the role of the SHH, TYR

or MYC molecular subgroups or germline SMARCB1/A4 mutations in the patient cohort.

In previous years, the importance of epigenetic markers in carcinogenesis has been reported in relation to understanding the mechanisms of metastatic tumor progression. Both the upregulation and downregulation of microRNAs result in increased cell proliferation, tumor invasion and interaction with various driver markers. A number of different microRNAs have been shown to be useful at both diagnostic and prognostic levels (17).

Further research is required into targeted therapy of ATRT specific to each molecular subtype (TYR, SHH and MYC), as the outcome is still poor using the currently available therapeutic options of standard chemotherapy, radiation therapy, surgery and high-dose chemotherapy. Torchia *et al* (18) reported that cell lines derived from ATRT-SHH tumors were highly sensitive to enhancer of zeste homolog 2 inhibitors (18). Although subtype-specific targeted therapy is still in the early phases of clinical trials, the preliminary results may indicate improved outcomes of this aggressive disease. Delineating prognostic factors affecting the survival of ATRT is necessary for adequate disease management.

The treatment regimen should be dose-adjusted according to each patient to maintain the treatment intensity and to avoid toxicity-related mortality. The use of high-dose chemotherapy may be associated with improved outcomes and higher toxicity rates, necessitating timely supportive care, especially in lower- and middle-income settings. Further clinical trials incorporating novel targeted therapies are required in the future.

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#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Authors' contributions

AEHe conceived the present study. MSZ and AEHe confirmed the authenticity of all the raw data MS collected data and participated in designing the study. EM and MSZ performed data analysis and validation. AEHa drafted the manuscript and interpreted the data. HT, AR and MEB analyzed the data. AEHa and MSZ gave the final approval of the version to be published. All authors have read and approved the final manuscript.

#### Ethics approval and consent to participate

The present study was conducted in accordance with The Declaration of Helsinki. Ethics approval was provided by the institutional review board of the Children's Cancer Hospital of

Egypt 57357 (approval no. 28-7-2021; Cairo, Egypt) and the requirement for obtaining written consent was waived due to the retrospective nature of the present study.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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