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RESEARCH ARTICLE

Outcomes for children with recurrent/refractory atypical teratoid rhabdoid tumor: A single-institution study with molecular correlation

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Abstract

Background: Survival data for recurrent pediatric atypical teratoid rhabdoid tumor (ATRT) and its association to molecular groups are extremely limited.

Methods: Single-institution retrospective study of 64 children less than 21 years old with recurrent or treatment-refractory (progressive disease [PD]) ATRT treated at St. Jude Hospital from January 2000 to December 2020. Demographic, clinicopathologic, treatment, molecular grouping (SHH, TYR, and MYC) and germline data were collected. Progression-free survival (PFS2: time from PD to subsequent first progression) and overall survival (OSpostPD: time from PD to death/last follow-up) were estimated by Kaplan–Meier analysis.

Results: Median age at and time from initial diagnosis to PD were 2.1 years (range: 0.5–17.9 years) and 5.4 months (range: 0.5–125.6 months), respectively. Only five of 64 children (7.8%) are alive at median follow-up of 10.9 (range: 4.2–18.1) years from PD. The 2/5-year PFS2 and OSpostPD were 3.1% (±1.8%)/1.6% (±1.1%) and

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; CSI, craniospinal irradiation; GLA, germline alteration; OSpostPD, overall survival following recurrence; PD, progressive disease; PFS2, progression-free survival following recurrence; RT, radiation therapy.

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20.3% (±4.8%)/7.3% (±3.5%), respectively. Children with TYR group ($n = 10$) had a better OSpostPD compared to those with MYC ($n = 11$) (2-year survival estimates: 60.0% ± 14.3% vs. 18.2% ± 9.5%; $p = .019$), or those with SHH ($n = 21$; 4.8% ± 3.3%; $p = .014$). In univariate analyses, OSpostPD was better with older age at diagnosis ($p = .037$), female gender ($p = .008$), and metastatic site of PD compared to local or combined sites of PD ($p < .001$). Two-year OSpostPD for patients receiving any salvage therapy ($n = 39$) post PD was 33.3% ± 7.3%.

Conclusions: Children with recurrent/refractory ATRT have dismal outcomes. Older age at diagnosis, female gender, TYR group, and metastatic site of PD were associated with relatively longer survival in our study.

KEYWORDS
ATRT germline variants, ATRT molecular groups, ATRT survival, recurrent ATRT

1 | INTRODUCTION

Atypical teratoid rhabdoid tumor (ATRT) is a rare but devastating childhood cancer with few successful treatment options. Affected children are often treated with a combination of surgery, chemotherapy, and radiation therapy (RT) at their initial diagnosis. A consensus on the "best" standard of care for pediatric ATRT remains elusive, with different multi-institutional or co-operative group trials reporting similar success rates largely determined by the age and metastatic status at diagnosis, and the field of radiation employed.[1–4] While molecularly targeted therapies are making their way into the treatment plan for these children, they are yet to show a curative benefit.[5–7] Children who fail their upfront treatment have very limited therapy options. However, there are extremely limited data on the survival of children with recurrent or treatment-refractory ATRT and their association with the three molecular groups described: ATRT-MYC (MYC), ATRT-SHH (SHH), and ATRT-TYR (TYR). Recently reported clinical trials and registry study results suggest that the TYR group may have a more indolent growth and better overall survival compared to the MYC or SHH groups[2,4] among patients receiving frontline therapies. Thus, these reports need to be validated in future studies. Additionally, approximately 25%–30% of children with ATRT have a germline heterozygous alteration in the *SMARCB1* or *SMARCA4* genes, resulting in rhabdoid tumor predisposition syndrome (RTPS), a cancer predisposition state. However, its impact on treatment response and survival is yet to be clearly defined.[1,2,4,8,9]

We undertook a single-institution retrospective study of children with histologically confirmed ATRT treated at St. Jude Children's Research Hospital, Memphis, USA (St. Jude) that had failed frontline therapies, analyzing their survival and its correlation to the three ATRT molecular groups and to the presence of underlying cancer predisposition state. Additionally, we sought to determine the clinicopathological and treatment features, if any, that correlate with outcomes in these children.

2 | METHODS

2.1 | Study population

Pediatric patients ≤21 years-old with recurrent/treatment-refractory ATRT treated at St. Jude from January 1, 2000 to December 31, 2020 were eligible for this retrospective single-institutional study. Histopathologic confirmation of ATRT was performed on all eligible patients either at diagnosis, recurrence, or both. Tumor nuclear INI loss was confirmed when tumor sample was available to perform the test. A patient's tumor was defined as "recurrent" when new lesions were identified on imaging or if the cerebrospinal fluid (CSF) analysis was positive for ATRT, following completion of all therapy at initial diagnosis. "Refractory" tumor was defined as tumor that progressed while receiving front-line therapy, resulting in alternative management due to treatment failure. Hence forth, the term progressive disease (PD) will be used to include both recurrent and treatment-refractory cases in our study.

Tumor DNA methylation, molecular grouping, and germline analysis for available samples were completed as detailed previously.[2] All patients with adequate tumor tissue for DNA methylation profiling and paired germline samples were included in the molecular analyses, and the associated patient outcomes were correlated to molecular group and pathogenic or likely pathogenic (P/LP) germline alterations (GLA), including the presence of germline *SMARCB1/SMARCA4* variants.

Clinical data were obtained from patient records and included, among other variables, age at first diagnosis, gender, race, tumor location at initial diagnosis, metastatic status at diagnosis and at PD, age at PD, salvage therapies used, and date of death, or last follow-up until

October 1, 2022. The St. Jude institutional review board reviewed and approved this study.

2.2 | Statistical analysis

As the terms progression-free survival and overall survival are traditionally used to describe outcomes for patients with newly diagnosed cancers, we opted to use progression-free survival after recurrence/progression (PFS2) to define the time interval from date of initial PD to the earliest date of subsequent disease progression or death, or to the date of last follow-up for patients without events. Similarly, overall survival after initial recurrence/progression (OSpostPD) was defined as the time interval from date of initial PD to the date of death for patients who died, or to date of last follow-up for survivors.

Fisher's exact tests were used to examine associations between categorical variables. Survival estimates and Kaplan–Meier curves were provided. Differences in survival distributions were examined by log-rank tests. Potential predictor variables considered in survival analyses included age at initial diagnosis (<1 vs. ≥1 year), gender (female vs. male), duration from initial diagnosis to PD (<2 vs. ≥2 years), site of PD (metastatic vs. others that involved local sites of relapse), molecular groups, and GLA (positive vs. negative). A significance threshold of .05 was used without adjusting for multiplicity. All *p*-values were two-sided. Analyses were performed using SAS, version 9.4 (SAS Institute).

3 | RESULTS

3.1 | Patient characteristics

A total of 183 patients with ATRT were treated at St. Jude from January 1, 2000 to December 31, 2020. Of these, 64 patients had PD and met inclusion criteria. Patients who transferred care or did not have further follow-up after PD at St. Jude were excluded from the study. Histopathological review for confirmation of tumor *INI-1/BRG-1* (Brahma-related gene 1) loss was established in 63/64 patients, including 16 patients who had this confirmed at the time of disease recurrence. Patient demographics, tumor location, metastatic status at initial diagnosis, molecular group, and presence of GLA are presented in Table 1. Over 75% of the patients were less than 3 years old (median age: 1.5 years [range: 0.0–17.1]), with 34% less than 1 year of age at initial diagnosis. Nearly two-thirds of the patients presented with nonmetastatic disease at diagnosis. In addition to surgery, upfront treatment included chemotherapy only in 35 (54.7%) and chemoradiotherapy in 27 (42.2%). Two patients received only RT. Of those receiving RT at initial diagnosis, craniospinal irradiation (CSI) was used in 12 patients (41.4%).

Molecular grouping information was available for 42/64 patients (66%), with a majority belonging to the SHH subtype (Table 1). Germline data were available for 35/64 patients (55%), of which 13 patients (37%) were found to have a GLA of either *SMARCB1* ($n = 7$) or other cancer predisposition genes ($n = 6$) (Table S2).

TABLE 1 Patient/tumor characteristics ($n = 64$).

Variable	No. (%)
Age at first diagnosis, years	
Median (range)	1.5 (0.0–17.1)
Sex	
Female	35 (55)
Male	29 (45)
Race	
White	45 (70.3)
Black	5 (7.8)
Asian	5 (7.8)
Mixed/multiple/other	9 (14.1)
Age group at diagnosis	
<1 year	22 (34.4)
1 to <3 years	27 (42.2)
≥3 years	15 (23.4)
Molecular groups	
ATRT-MYC	11 (26.2)
ATRT-SHH	21 (50.0)
ATRT-TYR	10 (23.8)
NA	22
Germline alterations	
Positive	13 (37.1)
Negative	22 (62.9)
NA	29
Metastatic status at diagnosis	
M0	41 (64.1)
M1	3 (4.7)
M2	7 (10.9)
M3	13 (20.3)
Primary tumor site at diagnosis	
Supratentorial	30 (46.9)
Infratentorial	31 (48.4)
Spinal	3 (4.7)
Time to PD, months	
Median	5.4
Range	0.5–125.6
Site of initial PD	
Local	13 (20.3)
Metastatic	32 (50.0)
Local/metastatic	18 (28.1)
2nd Primary tumor	1 (1.6)

Abbreviations: NA, not available; PD, progressive disease.

3.2 | Pattern of PD and salvage therapy used

The median time from initial diagnosis to PD was 5.4 months (range: 0.5–125.6 months), and the median age at PD was 2.1 years (range: 0.5–17.9 years). An overwhelming majority (78%) of the patients had a metastatic component at the time of PD. Half of the patients in our study had an isolated metastatic recurrence after having achieved complete remission of their disease. Only 20% of the patients had isolated localized PD. A second primary tumor was found in one patient (Patient #39, Table S1). The median number of progressions was 2 (range: 1–9). Salvage therapies included chemotherapy/molecular targeted therapy only (n = 17, 27%), a combination of chemotherapy/molecular targeted therapy and RT (n = 20, 31%), and RT only (n = 2, 3%). Twenty-five patients (39%) received palliative care/symptom management only with no further antitumor therapy, especially those with early PD. CSI was employed as part of salvage treatment regimen in nine patients, either after the first (n = 5) or second (n = 4) instance of PD.

3.3 | Outcomes

The median time from PD to subsequent progression (PFS2) was only 3.2 months (range: 0.6–38.2). The 2- and 5-year PFS2 were 3.1% (±1.8%) and 1.6% (±1.1%), respectively (Figure 1A). Only one patient (Patient #2, Table 2) did not experience further progression of disease at last follow-up at 16.4 years. OSpostPD was dismal, with 59/64 patients dying from their disease. The median survival time from PD to death was 4.2 months (range: 0.2–55.0 months). The 2- and 5-year OSpostPD estimates were 20.3% (±4.8%) and 7.3% (±3.5%), respectively (Figure 1A). Only five patients (7.8%) were alive at last follow-up, with median follow-up of 10.9 years (range: 4.2–18.1 years) from first PD (Table 2). PD following upfront CSI at initial diagnosis was particularly devastating with all (n = 12) patients succumbing to the disease compared to those who did not receive CSI at initial diagnosis (n = 52).

Multiple factors were noted to be associated with survival in our cohort (Figure 1). OSpostPD was better in children who were older than 1 year at diagnosis (p = .04) and in female patients (p = .008). However, there was no evidence in our study suggesting an association between relapse duration from diagnosis (<2 years, n = 57 vs. ≥2 years, n = 7) and OSpostPD (p-value = .137). This result though must be interpreted with caution due to the small number of patients in PD greater than 2 years from diagnosis group. Outcomes were better in children with metastatic PD compared to local only or combined local and metastatic sites of PD (2-year OSpostPD of 37.5% [±8.2%] vs. 3.2% [±2.2%]; $p \leq .001$) (Figure 1D). Furthermore, we tested the association between the site of PD and prior RT. Among patients who had undergone focal RT at their initial diagnosis and prior to PD, there was a higher proportion of patients with metastatic site of relapse, compared to those who had not (71.4% vs. 34.3%, p = .005).

ATRT molecular group affiliation was notable for an improved outcome in children with TYR group having a significantly better 2-year overall survival (60.0 [±14.3%]) compared to MYC (18.2 [±9.5%]) or SHH group (4.8 [±3.3%]) (Figure 1E). No significant difference in OSpostPD was found with respect to the presence of underlying GLA in known cancer predisposing genes (p = .230; Table S2).

Next, we investigated differences in OSpostPD between patients who received "any" salvage therapy at the time of their first PD (n = 39) versus those who had palliative care or symptom management only without definitive antitumor therapies (n = 25). The 2- and 5-year OSpostPD for patients who received salvage treatment post PD were estimated to be 33.3% (±7.3%) and 12.0% (±5.6%), respectively (Figure 2A). All patients who received only palliative care post PD passed away shortly, with a median time from PD to death of 1.1 months (range: 0.2–4.6 months). Further, within the salvage treatment group (n = 39), while there was no difference in OSpostPD by age at diagnosis (<1 vs. ≥1 year), outcomes differed by gender, site of PD (metastatic only vs. others), and by molecular group (TYR vs. rest) similar to that observed for the entire study cohort (n = 64) (Figure 2B–E).

3.4 | Clinicopathologic features of survivors at the time of analysis

Five patients are alive at the time of this analysis, having received different salvage regimens, including RT in all (CSI-2, Focal-3) (Table 2). Patient #4, in addition, had sustained response to alisertib prior to having further PD and has been previously reported as part of the SJATRT A1 stratum trial results.[6] In addition, three of four of the survivors with available molecular group information belonged to the TYR group and three patients had a *SMARCB1* GLA. Pertinent clinicopathologic and treatment details for the remaining 59 patients who are deceased are summarized in Table S1.

Nine children in the current study received CSI post PD. Of these, two are long-term survivors (Table 1), while the remaining seven have succumbed to the disease. The median time to death from CSI in these seven patients was 21.6 months (range: 0.4–37.0 months).

4 | DISCUSSION

Survival outcomes for children with recurrent or treatment-refractory ATRT are dismal, as evidenced by our single-center retrospective study. Outcomes are especially poor for those with a young age at initial diagnosis and non-TYR molecular groups, while those with metastatic site of PD seemed to benefit from salvage therapies. The presence of germline pathogenic alterations of cancer predisposition genes did not significantly alter outcomes for these children. Outcomes were particularly dismal for children who had recurrence following initial CSI. Salvage therapies at PD benefited some patients, but there are only a very limited number of long-term survivors in the current study who received a combination of chemo-radiotherapy and targeted therapy. The benefit, if any, of salvage therapies on survival must be interpreted with caution, as the decision to undergo further salvage treatment may have depended on, among other factors, family

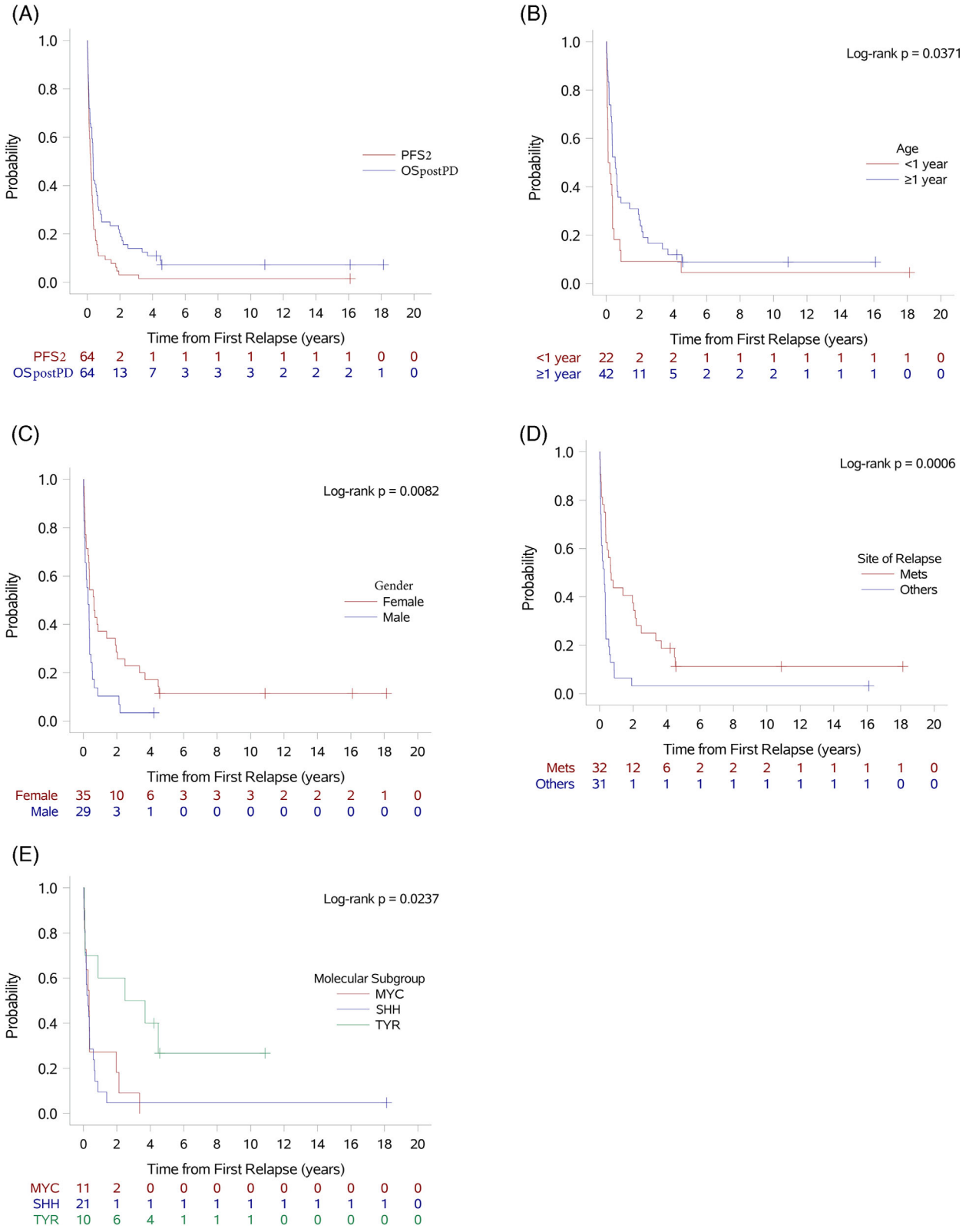


FIGURE 1 Kaplan–Meir survival curves for all patients. Five-year PFS2 and OSpostPD for all 64 participants (A). Five-year OSpostPD by age <1 year versus >1 year at diagnosis (B), gender (C) site of relapse (D) and molecular group (E). PD, progressive disease; PFS2, time from initial PD to subsequent progression; OSpost PD, time from initial PD to the date of death or date of last follow-up; mets, metastatic disease; MYC, ATRT-MYC; SHH, ATRT-SHH; TYR, ATRT-TYR.

TABLE 2 Clinicopathologic characteristics of survivors at the time for analysis.

Patient #	Age at diagnosis (years)	Metastatic status at diagnosis	Molecular grouping	Germline alteration	Initial treatment	Time to 1st progression (years)	Site of 1st progression	Age at 1st progression (years)	Post-progression treatment	Follow-up from 1st progression (years)
1	0.56	M0	SHH	Positive	PBTC001[25]	0.9	Mets	1.49	(1st) Surg, P9962[26] (2nd–4th) Surg/gamma knife (5th) PBTC016[27] (lapatinib) (6th) PBTC17[28] (cloretazine) (7th) Temsirolimus[29] (8th) Surg/oxaliplatin/etoposide[30] (9th) Surg/focal RT	18.1
2	1.07	M0	NA	Positive	NPTP PBTC001[25]	0.3	Local	1.34	Surg, topo/cyclo[2] focal RT	16.4
3	1.63	M0	TYR	NA	NPTP SJYC07[2]	1.1	Mets	2.68	(1st) Surg, ICE/vorinostat 13-cis retinoic acid[31] (2nd) CSI	10.9
4	1.46	M0	TYR	Positive	SJYC07[2]	1.8	Mets	3.22	(1st) SJATRT alisertib[6] (2nd) spinal RT, ICE[32]	4.6
5	1.25	M2	TYR	NA	NPTP SJYC07[2]	0.9	Mets	2.14	(1st) SJATRT alisertib[6] (2nd) CSI	4.1

Abbreviations: CSI, craniospinal irradiation; ICE, ifosfamide, carboplatin, etoposide; mets, metatstatic; NA, not available; NPTP, non-protocol treatment plan; RT, radiotherapy; surg, surgery.

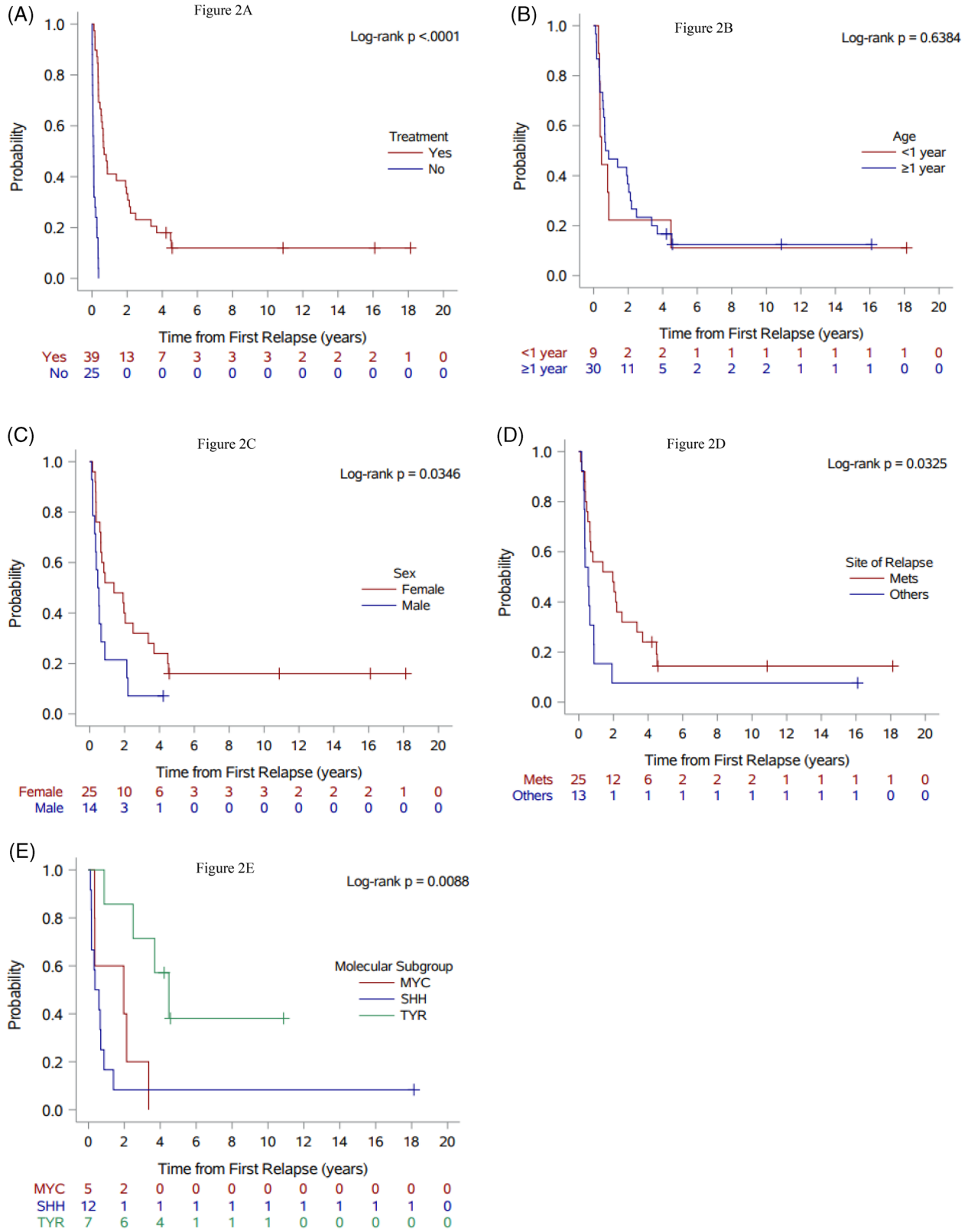


FIGURE 2 Kaplan–Meir survival curves for patients by treatment received post PD. Five-year OSpostPD for patients who received any salvage therapies post PD (Yes) ($n = 39$) versus palliative care only (No) ($n = 25$) (A). Five-year OSpostPD by age <1 year versus >1 year at diagnosis (B), gender (C) site of relapse (D) and molecular group (E) for patients receiving salvage therapies subsequent to PD. PD, progressive disease; OSpost PD, time from initial PD to the date of death or date of last follow-up; mets, metastatic disease; MYC, ATRT-MYC; SHH, ATRT-SHH; TYR, ATRT-TYR.

and provider preference and performance status of the patient and hence, prone for selection bias.

ATRT is an aggressive central nervous system malignancy that primarily affects young children. Despite the advances in our understanding of the biology of the tumor, there has been very limited success in treating this devastating cancer with a reported 4–5-year overall survival of 40%–50% by most cooperative groups or multi-institutional clinical trials in children with newly diagnosed ATRT.[1–4] Moreover, there is extremely limited literature on survival outcomes in children with relapsed or progressive ATRT, which is a clear indication of the paucity of treatment options for these children.[6,7,10–12] This single-institution study is the largest to date to report on outcomes for children with recurrent or progressive ATRT who have failed at least one frontline therapy in addition to surgery. Our study identifies a very limited set of clinicopathologic and molecular features that are associated with long-term survival. Among these are the metastatic site of tumor recurrence, which may present opportunities for salvage radiation to the site of recurrence, including the possibility of CSI in older children. As is evident from Table 2, all our current survivors received RT at recurrence, either focal or CSI. While it is not possible to make concrete recommendations on the field of RT to be used in those with metastatic failure due to the limited number of long-term survivors in our study, emerging data suggest that radiation is a useful modality for tumor control in children with ATRT. It is also pertinent to note that even though the majority of those who received CSI as salvage therapy eventually died from the disease (7/9), survival was prolonged to a median of 21.6 months with the use of CSI in these patients. Additionally, two patients who received CSI as part of salvage therapy are alive at the time of this report, 10.6 and 4.1 years from their PD.

Treatment protocols using a chemotherapy-only approach have resulted in very limited success for children with ATRT.[13–18] We have previously reported on the use of trimodal therapy, including risk-stratified use of RT in children with newly diagnosed ATRT, with very good outcomes in children greater than 3 years of age at diagnosis and nonmetastatic ATRT with the use of postoperative CSI and adjuvant chemotherapy. Other studies have suggested that the use of response-based focal RT in those with complete response to chemotherapy is not inferior to CSI while avoiding the long-term consequences of CSI in young children.[18,19] What is unclear, though, is if this use of response-based RT and avoiding CSI in patients with newly diagnosed ATRT will eventually preclude the use of more extensive field and repeat salvage RT in the unfortunate event of disease recurrence. A recent study by Johann et al.[20] revealed differentially expressed genes in primary and recurrent ATRT, thus suggesting that additional molecular changes develop at the time of PD. It remains to be determined though, if such transcriptomic and molecular differences result in a clinically more aggressive and treatment-refractory disease in a tumor that is already difficult to cure at the time of initial diagnosis.

ATRT is molecularly divided into at least three groups—SHH, TYR, and MYC, with additional subtypes, primarily in the SHH group being recently described. Results from clinical trials suggest that the TYR group of patients may present with more indolent growth with a relatively better overall survival compared to the other two groups.[2,4] Our study reveals that this relatively better outcome for those with TYR group is retained in the setting of recurrent or PD. Our understanding of the biology underlying this indolent growth of the TYR group is yet to be identified. Apart from this, the emerging data on the different SHH types and their prognostic relevance are unclear, with studies demonstrating contradictory results.[21,22] However, what is clear from these studies is that ATRT is a biologically very heterogenous disease, both in its clinicopathologic features as well as in treatment response and survival outcomes.

Although the survival outcome is generally gloomy, there are reports in the literature, including the current study, of limited treatment success in children with recurrent or progressive ATRT.[6,12,23,24] Given its rarity and the widely different treatment regimens employed to treat ATRT, it will be vital to conduct a pooled analysis of such studies and, when possible, correlate it to molecular findings to better understand the clinicopathologic correlates associated with treatment success and recommendations on salvage therapies for these patients.

The underlying molecular, clinical, and survival data are accessible through the visualization portal at https://viz.stjude.cloud/st-jude-childrens-research-hospital/visualization/outcomes-for-patients-with-recurrentrefractory-atypical-teratoid-rhabdoid-tumor~1543 to allow for custom queries. The limitations of our study are its retrospective nature, single-institution cohort, and inability to recommend any specific type of salvage therapy due to a small number of survivors in the present study and its descriptive nature. However, this study provides objective background information on survival for children with recurrent ATRT that can be used as a foundation to draft and set goals for future clinical trials.

5 | CONCLUSIONS

Recurrent/progressive ATRT is most often a fatal disease with very few long-term survivors. While treatment at recurrence may prolong survival in some patients, there is a lack of effective salvage therapies for a majority. Older age at initial diagnosis, female gender, TYR molecular group, and metastatic site of PD were associated with relatively longer survival in our study. Recurrence after upfront CSI was associated with dismal outcomes, while there was no association with germline cancer predisposition variants and outcomes. Further understanding of the biological underpinnings of tumor development and response to therapy is crucial to improving outcomes for affected children.

AUTHOR CONTRIBUTIONS

Study design: Steven Carey, Santhosh A. Upadhyaya, Arzu-Onar Thomas, Jie Huang, Giles W Robinson, Thomas E. Merchant, Amar Gajjar. Data collection: Steven Carey, Santhosh A. Upadhyaya, Jason R. Myers, Roya Mostafavi, Brent Orr, Sandeep Dhanda, Layna H. Michalik, Ruth G. Tatevossian, Paul Klimo Jr., Frederick Boop, David W. Ellison, Giles W Robinson, Thomas E. Merchant, Amar Gajjar. Data analysis: Arzu-Onar Thomas, Jie Huang, Steven Carey, Santhosh A. Upadhyaya, Jason R. Myers, Roya Mostafavi, Sandeep Dhanda, Congyu Lu, Kim E.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The manuscript also offers a data portal that allows users to delve into details at the patient or cohort level. We have connected the clinical metadata information as a variable to facilitate personalized visualization of molecular data matrix plots and survival outcomes. The portal will be available for reviewer at the link: https://proteinpaint.stjude.org/?mass-session-file=files/hg38/recATRT/classification/recATRT2024.json and the password to access the portal will be stjuderecATRT.

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SUPPORTING INFORMATION

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