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SEQUENCING OF LOCAL THERAPY AFFECTS THE PATTERN OF TREATMENT FAILURE AND SURVIVAL IN CHILDREN WITH ATYPICAL TERATOID RHABDOID TUMORS OF THE CENTRAL NERVOUS SYSTEM

Atmaram S. Pai Panandiker, M.D.^{*}, Thomas E. Merchant, D.O., Ph.D.^{*}, Chris Beltran, Ph.D.^{*}, Shengjie Wu, M.S.[†], Shelly Sharma, M.D.^{*}, Frederick A. Boop, M.D.[‡], Jesse J. Jenkins, M.D.[§], Kathleen J. Helton, M.D.^{*}, Karen D. Wright, M.D.[¶], Alberto Broniscer, M.D.[¶], Larry E. Kun, M.D.^{*}, and Amar Gajjar, M.D.[¶]

^{*}Department of Radiological Sciences, St. Jude Children's Research Hospital, Memphis, TN

[†]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN

[‡]Department of Surgery, St. Jude Children's Research Hospital, Memphis, TN

[§]Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN

[¶]Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN

Abstract

Purpose—To assess the pattern of treatment failure associated with current therapeutic paradigms for childhood atypical teratoid rhabdoid tumors (AT/RT).

Methods and Materials—Pediatric patients with AT/RT of the central nervous system treated at our institution between 1987 and 2007 were retrospectively evaluated. Overall survival (OS), progression-free survival, and cumulative incidence of local failure were correlated with age, sex, tumor location, extent of disease, and extent of surgical resection. Radiotherapy (RT) sequencing, chemotherapy, dose, timing, and volume administered after resection were also evaluated.

Results—Thirty-one patients at a median age of 2.3 years at diagnosis (range, 0.45–16.87 years) were enrolled into protocols that included risk- and age-stratified RT. Craniospinal irradiation with focal tumor bed boost (median dose, 54 Gy) was administered to 18 patients. Gross total resection was achieved in 16. Ten patients presented with metastases at diagnosis. RT was delayed more than 3 months in 20 patients and between 1 and 3 months in 4; 7 patients received immediate postoperative irradiation preceding high-dose alkylator-based chemotherapy. At a median follow-up of 48 months, the cumulative incidence of local treatment failure was $37.5\% \pm 9\%$; progression-free survival was $33.2\% \pm 10\%$; and OS was $53.5\% \pm 10\%$. Children receiving delayed RT (> 1 month postoperatively) were more likely to experience local failure (hazard ratio [HR] 1.23, $p = 0.007$); the development of distant metastases before RT increased the risk of progression (HR 3.49, $p = 0.006$); and any evidence of disease progression before RT decreased OS (HR 20.78, $p = 0.004$). Disease progression occurred in 52% (11/21) of children with initially

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Reprint requests to: Atmaram S. Pai Panandiker, M.D., Department of Radiological Sciences, Mail Stop 220, St. Jude Children's, Research Hospital, 262 Danny Thomas Place, Memphis, TN, 38105-3678. Tel: (901) 595-3226; Fax: (901) 595-3113; atmaram.pai-panandiker@stjude.org.

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localized tumors who underwent gross total resection, and the progression rate increased proportionally with increasing delay from surgery to RT.

Conclusions—Delayed RT is associated with a higher rate of local and metastatic disease progression in children with AT/RT. Current treatment regimens for pediatric patients with AT/RT are distinctly age stratified; novel protocols investigating RT volumes and sequencing are needed.

Keywords

Atypical teratoid rhabdoid tumor; Local failure; Radiation therapy; Therapeutic sequencing; Pattern of failure

INTRODUCTION

Atypical teratoid rhabdoid tumor (AT/RT) is a rare, aggressive embryonal tumor commonly occurring in young children in both the brain and a variety of soft tissue sites outside the central nervous system (CNS). Although consensus exists regarding the epidemiology and molecular background of approximately 90% of cases (inactivating deletion or mutation of the *SMARCB1* gene found on chr22q11.2), therapeutic consensus remains to be defined because of the poor outcomes, especially in very young children (1–3).

The role of radiation therapy (RT) in the treatment of childhood CNS AT/RT is currently undefined, including the required dose, volume, and sequencing of irradiation as a component of multidisciplinary therapy (4). Current clinical trials designed to include children with AT/RT prescribe high-dose irradiation to the tumor bed, but they vary in their use of craniospinal irradiation (CSI) vs. focal RT and sequencing of irradiation and chemotherapy, despite presentations and patterns of treatment failure that seem to be similar to those of patients with other embryonal CNS tumors (5). Older children are often treated with immediate postoperative RT including CSI, but those younger than 3 years receive postoperative chemotherapy with or without delayed focal irradiation because of the adverse effects of CSI on the young developing brain (5–7).

Young age at the time of diagnosis of AT/RT is associated with poorer prognosis, and AT/RT is interpreted by some as a more aggressive neoplasm in the young. Therapy differs with age; however, young children are infrequently treated with CSI, and postoperative RT is typically delayed by at least 4 to 6 months of chemotherapy (4, 8–10). Whether the age-related differences in disease control reflect biology or the omission of CSI and/or delay in RT can be assessed by comparing the incidence and pattern of treatment failure in patients who received CSI with those measures in patients who received focal irradiation; analysis accounting for the timing of irradiation is also necessary.

Recent studies have suggested the importance of postoperative RT, including the influence of total dose and treatment volume, on local tumor control and survival. The influence of timing on overall survival (OS) has also been demonstrated. Chen *et al.* showed that the total dose affects failure-free survival and that OS is influenced by the interval of time between surgical resection and the initiation of RT (5). Chi *et al.* showed no long-term survivorship in the subset treated without RT; of the long-term survivors, all received postoperative RT (6).

We previously reported on 37 patients with AT/RT treated with combined modality therapy including surgery, RT, and chemotherapy (7). The event-free survival was $11\% \pm 6\%$ for the 22 children younger than 3 years at diagnosis and $58\% \pm 19\%$ for the 9 older children who were uniformly treated with postoperative CSI. Two long-term survivors (*i.e.*, those surviving more than 24 months from diagnosis) in the younger cohort received RT early in

their treatment course, before progressive disease developed and while they were receiving chemotherapy.

In this report, we update our institutional experience for patients who received RT with the goal of using a competing risk strategy in our analysis to identify tumor- and treatment-related factors that predict the pattern of failure and outcome in these patients. We further seek to demonstrate that in this dataset, most young children with AT/RT present with non-metastatic disease, and short-interval postoperative focal irradiation may cure AT/RT in some of this group. However, the potential risk/benefit profile of this approach cannot be demonstrated without further clinical investigation.

METHODS AND MATERIALS

We retrospectively reviewed the medical records of 35 pediatric patients with CNS AT/RT treated at St. Jude Children's Research Hospital during a 20-year period (1987–2007). Some patients with CNS AT/RT were excluded from this analysis because of rapid progression during adjuvant chemotherapy and obviation of RT. The combined modality therapies used included surgical resection, various combinations of adjuvant chemotherapy, and RT administered either on prospective institutional trials or by using a best clinical management strategy. We did not include in our analysis any patients who were enrolled in yet unreported frontline protocols after 2003. Four patients were not included because they did not receive RT at our institution ($n = 2$), or the pattern of treatment failure imaging was either not performed or unavailable at our institution ($n = 2$). Thus, 31 children were evaluable for pattern of failure and local control analyses. This study was approved by the St. Jude institutional review board.

Central pathologic review of tumor samples confirmed the diagnosis of AT/RT in each case. The *SMARCB1* gene is typically inactivated by mutation or deletion in malignant rhabdoid tumors (11). Thus, we confirmed either negative *SMARCB1* status or BAF47-negative immunohistochemistry in each case (12). The following clinical variables were obtained for each patient: age at diagnosis; sex; tumor location; extent of surgical resection; RT timing, dose, and volume (CSI and/or focal); sequence of therapy; and chemotherapy regimens.

The statistical endpoints for this retrospective study were the Kaplan-Meier estimates of PFS and OS measured from the start of RT (13). PFS was measured from the date of starting RT to the date of post-RT disease progression, inclusive of infield failure, distant failure, and death; PFS was not measured from date of diagnosis because of a primary interest in the impact of RT treatment effect relative to delayed start. OS was measured from the date of initial diagnosis of AT/RT to the date of death or last known contact. Treatment failure after RT was defined as recurrence of the primary tumor and/or metastasis to the neuraxis. If a lesion was noted as possible progression or metastasis, it was followed until progression was confirmed, and the date that the initial lesion was noted on MR imaging was considered the date of failure. Relevant to intracranial progression and the assessment of local vs. distant treatment failure, the imaging that demonstrated first failure after RT was registered to the original planning computed tomography images. The criteria for establishing infield failure were chosen based on 80% or more of the volume of the lesion being contained within the 95% isodose volume. First-failure volumes in which 20% to less than 80% of the tumor was contained within the 95% isodose line were considered marginal failures. The cumulative incidence of local failure was defined by the first infield failure. The Cox proportional hazard model was used to investigate prognostic risk factors for PFS and OS (14). The cumulative incidence of local treatment failure was calculated using Gray's method (15). The cumulative incidence of failure was measured from the first day of irradiation to the date of first failure, and any other failures occurring before the failure were considered

competing events. Fine's method was used to evaluate prognostic risk factors for the cumulative incidence of local failure (16).

RESULTS

Patients

The median age at diagnosis for these 31 patients was 2.3 years (range, 0.45–16.87 years); 19 patients were younger than 3 years. The cohort included 15 boys and 16 girls. The tumor location was infratentorial in 15 patients, cerebral hemispheric in 12, and central in 4. Metastatic disease was present at diagnosis in 10 patients, and gross total resection (GTR) was achieved in 16 (Table 1).

Three patients presented with synchronous or metachronous rhabdoid tumors of the kidney, adrenal gland, and skin, and 1 other patient developed a secondary spinal intradural, extramedullary AT/RT infield 4.5 years after chemotherapy and involved-field RT for Hodgkin lymphoma. Among the 10 patients with metastatic disease at diagnosis, 9 presented with imaging evidence of leptomeningeal spread, including 5 patients with nodular metastases. One patient presented with cytologic evidence of dissemination in the cerebrospinal fluid alone.

Preirradiation therapy

The RT was delayed more than 3 months after definitive surgery in 20 patients; 18 of these children were younger than 3 years of age. Of these 20, 6 children experienced progressive local disease after undergoing GTR, with a median time to progression of 3.3 months (range, 1.1–8.2 months). Nineteen of the 20 patients received chemotherapy before RT. One patient who did not receive chemotherapy before RT had undergone GTR; progression of disease at the primary site occurred during the 14-week postoperative period before RT while the patient was undergoing rehabilitation at an outside facility. Among the 19-patient subset, 7 had metastatic disease at diagnosis (4/7 died of progressive disease), and 13 overall experienced disease progression (Table 2). All 13 experienced local progression, and 6 developed concurrent distant progression.

Twenty-three of the 31 patients received preirradiation chemotherapy; 19 received chemotherapy for ≥ 3 months, and 4 received chemotherapy for <3 months. Five of these 23 completed chemotherapy with no evidence of disease progression; 3 demonstrated stable disease or had a less than complete response to chemotherapy; and 14 of these 23 children experienced progressive disease during chemotherapy. The 14 children with progressive disease experienced a median time to progression of 3.2 months (range, 0.9–5.9 months). One experienced progression in < 1 month, 2 in >1 but < 2 months, 2 in ≥ 2 but < 3 months, 4 in ≥ 3 but < 4 months, and 4 between months 4 and 6 of chemotherapy (Fig. 1).

Radiation therapy

Of the 12 patients older than 3 years, 5 received RT within 31 days of surgery, and 7 received delayed RT (> 1 month postoperatively) after a median delay of 2.5 months (range, 1.2–7.0 months). Of the remaining 5 children older than 3 years of age, all received RT within 31 days of operation followed by high-dose alkylator-based chemotherapy and were enrolled in the same previously reported institutional protocol (17). CSI with a median dose of 27 Gy was administered to 18 patients (range, 18–39.6 Gy); 6 of these children were younger than 3 years of age, and each received CSI shortly after experiencing metastatic progression; the median primary site dose was 54 Gy (range, 30.6–66.6 Gy) (Table 1). Among the 19 children younger than 3 years of age, all received RT >1 month after surgery

(range, 1.8–21.0 months) with a median dose of 54 Gy (range, 30.6–55.8 Gy); 13 received focal irradiation, and 5 received CSI.

Progression-free and overall survival after radiation therapy

At a median follow-up of 48 months (range, 4–189 months), the PFS of our cohort was $33.2\% \pm 10\%$, and OS was $53.5\% \pm 10\%$ (Fig. 2). Clinical factors were assessed for their impact on PFS by univariate Cox modeling: delay from diagnosis to initiation of RT (hazard ratio [HR] 1.13, $p = 0.05$); progression in the setting of GTR before irradiation (HR 4.68, $p = 0.003$); development of distant metastases before irradiation (HR 3.49, $p = 0.006$); conversion from STR to no evidence of disease before RT (HR 0.16, $p = 0.004$); and the use of high-dose alkylator-based chemotherapy (HR 0.19, $p = 0.03$) (data not shown). Patients who underwent GTR at diagnosis (HR 0.44, $p = 0.07$) and those who had stable disease before RT (HR 0.16, $p = 0.004$) were less likely to experience an adverse event; those for whom irradiation was delayed were more likely to experience an event (HR 1.13, $p = 0.05$) (Table 3).

When age at diagnosis and interval from diagnosis to initiation of RT were included in the regression model for all patients, the only factor to influence OS was evidence of local or distant disease progression during chemotherapy or during the period before RT (Table 4). Patients who underwent GTR were less likely to die than were those who had residual disease after surgery (HR 0.24, $p = 0.04$) (Table 5). Notably, metastatic disease at initial presentation did not significantly impact PFS or OS on univariate analysis. Therefore, subsequent multivariate analysis excluded this variable.

Cumulative incidence of postirradiation local treatment failure

Considering competing risks, the cumulative incidence of local treatment failure was $19.4\% \pm 7\%$ at 1 year and $37.5\% \pm 9\%$ at 4 years (Fig. 3). Children receiving less than GTR experienced local failure at a rate of $53.3\% \pm 14\%$ at 4 years follow-up, and those obtaining GTR had a local failure rate of $17.9\% \pm 10\%$. When age at diagnosis was included in the regression model, the factors influencing cumulative incidence of local treatment failure included radiation volume, extent of resection, and time from diagnosis to initiation of RT. Children younger than 3 years of age who received CSI (HR 4.78, $p = 0.06$) and delayed irradiation (HR 1.23, $p = 0.007$) were more likely to experience local failure, and those who underwent GTR (HR 0.24, $p = 0.04$) were less likely to experience local failure (Table 5).

Eleven of 21 (52%) patients with nonmetastatic disease at diagnosis experienced local or disseminated failure either while receiving chemotherapy or during a protracted period before RT. CSI was included in two treatment paradigms; 12 patients received delayed (>1 month postoperatively) CSI without high-dose alkylator-based chemotherapy, after local or metastatic progression of disease. Seven patients older than 3 years received CSI within 31 days of resection; CSI was followed by high-dose alkylator-based chemotherapy. Of those receiving immediate postoperative CSI, 29% (2/7) experienced local failure relative to 58% (7/12) of those receiving delayed postoperative CSI.

DISCUSSION

Children younger than 3 years who have brain tumors constitute a particularly vulnerable population for whom aggressive RT must be limited because of its adverse long-term effects. Historically, young patients with AT/RT have had a poor outcome; thus, concern about late effects must be balanced against poor prognosis (4, 17–19). In this retrospective analysis, we evaluated 31 pediatric patients with AT/RT who received combined modality therapy. We assessed the impact of the tumor and of clinical and therapeutic factors on local

control, PFS, and OS. Despite localized disease presentation in 68% (21/31) of patients, disease progression occurred in 55% (17/31) while they were receiving chemotherapy. Progression during chemotherapy correlated significantly with poor outcome.

Clinical management of AT/RT in North America differs by institution and cooperative group. These differences include chemotherapy regimens, dosing of alkylating agents, and administration of RT (8–10, 20). However, to our knowledge, no current or past protocol has addressed the possibility of immediate postoperative focal irradiation in children younger than 3 years with nonmetastatic disease at presentation. Current studies of patients in early childhood seek to avoid immediate postoperative RT. The 64% local failure rate observed in children receiving low- or standard-dose alkylator-based chemotherapy and delayed CSI results from the prevailing therapeutic model for very young children. It is difficult to define a clear role for high-dose alkylator-based chemotherapy alone in older children who experience a relatively low 1-in-3 risk of local failure while also receiving immediate postoperative irradiation.

Among the 19 children younger than 3 years, 14 experienced treatment failure. Six received CSI after experiencing progression with metastatic dissemination on chemotherapy; 8 experienced local progression during chemotherapy and received focal irradiation. Notably, 6 children younger than 3 years are alive with either no evidence of disease or with disease at last follow-up, all having received focal irradiation. These results are suggestive of a heterogeneous population with very different outcomes and few currently discernible factors of predictive value. They also suggest that a currently unclassified population would benefit from early focal irradiation.

Negative neuraxis imaging in the presence of microscopic disease in the cerebrospinal fluid at initial diagnosis did not significantly affect PFS or OS in univariate analyses. Multivariate analysis with Cox regression modeling subsequently revealed that the most relevant independent factors affecting PFS were extent of resection, time from diagnosis to initiation of RT, and age at diagnosis. Cox regression modeling for variables affecting OS demonstrated similar factors, including disease progression before RT initiation, time from diagnosis to RT initiation, and age at diagnosis. Although extent of resection affected PFS, it did not affect OS. This may reflect the small sample size analyzed and the fact that the population consisted of two very different therapeutic groups based on age stratification, which further limited power.

The 4-year PFS of 33.2% and OS of 53.5% observed in our patients represent an improvement when compared with those measures recently reported in other CNS AT/RT studies (5, 6). Univariate analysis of clinical factors, tumor characteristics, and therapeutic variables revealed a partial view of commonly investigated factors without excluding competing risks, which would alter the relative importance of each. Acceptable therapeutic plans direct different approaches based on age, with a bias toward assuming superior efficacy with CSI, when age allows or when dissemination demands it; however, the outcomes in this dataset do not support this hypothesis. We found that delay of RT negatively affected survival in this patient population; thus, we suggest that upfront focal irradiation be included in future protocols for children younger than 3 years with localized disease presentation to assess treatment outcomes and elucidate the differences between focal RT and CSI in different age groups.

This dataset included patients treated on multiple age-stratified protocols; of the patients older than 3 years, nearly half were treated on an institutional protocol requiring radiotherapy within 31 days of resection (21). Nearly all of these children demonstrated long-term survivorship, except for 1 who presented with nodular and diffuse metastases.

Each of these children also received upfront postoperative CSI, and by design, these were also the only ones to receive high-dose alkylator-based chemotherapy. However, neither treatment affected the outcome in the child with nodular and diffuse metastases at presentation.

Review of our clinical series suggests that locoregional control of disease is crucial to improve OS in pediatric patients with CNS AT/RT. The natural history of CNS AT/RT suggests a steadily increasing frequency of progression during at least a 6-month period of chemotherapy without RT after maximal safe surgical resection. Locoregional treatment failure eventually led to fatal progression of disease in 38% of these cases. The remaining patients experienced either distant progression or a combination of distant and local disease progression. Enhanced early local control may improve survival for a substantial proportion of patients in whom distant failure did not contribute to early progression. Although patients receiving CSI, including 6 who were younger than 3 years, were at high risk for local treatment failure, this phenomenon seems to be singularly linked to the current standard in which most patients with distant dissemination during chemotherapy receive CSI despite not having presented with metastatic AT/RT.

Therapeutic management of AT/RT is nearing a crossroads as several clinical studies near completion and begin providing results to guide future therapy (8–10, 20). Evidence of severe cranial irradiation–induced toxicity associated with the use of aggressive large-field RT in a very young population is prevalent (22–25). These findings have guided current protocols away from early use of any RT and have resulted in the use of RT on a delayed basis. Chemotherapy is now often administered during the initial postoperative period; RT is administered only after evidence of disease progression during chemotherapy. Current evidence suggests that highly conformal focal irradiation to small volumes is feasible, results in well-defined limited toxicities, and may yield curative potential to the large subset of young children presenting with localized disease (26–30). Furthermore, germline inactivation or deletion of the *SMARCB1* gene is linked to modulating repressive chromatin structure and is the likely explanation for tumorigenesis (11). Development of a molecular therapy will be difficult in the short term because it is generally simpler to inhibit rather than to enhance the activity of a protein. In the interim, selective reevaluation of highly conformal RT in young children may improve overall outcome.

CONCLUSIONS

In pediatric patients with CNS AT/RT, delayed RT correlates strongly with tumor progression and decreased OS. Our analyses suggest that early postoperative RT may improve local disease control, especially in patients who do not present with metastatic disease. We observed a high rate of early locoregional treatment failure, regardless of the extent of surgical resection, which suggests the need for immediate postoperative RT. The increased hazard ratio associated with receiving CSI reflects selective bias against the use of immediate postoperative RT in young children, the majority of whom presented with localized disease. While experimental therapeutics are being developed we conclude that immediate postoperative focal irradiation should be considered in future clinical trials, specifically for young children with AT/RT and no evidence of metastases at diagnosis.

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Fig. 1.
Relative time to progression of disease (PD) and time to radiotherapy (RT) for 14 patients with progressive disease after receiving postoperative pre-RT chemotherapy.

Fig. 2.
Progression-free survival (solid line) and overall survival (dashed line) among 31 pediatric patients with atypical teratoid rhabdoid tumor of the central nervous system.

Fig. 3.
Cumulative incidence of local treatment failure after radiotherapy (RT) in 31 pediatric patients with atypical teratoid rhabdoid tumor of the central nervous system.

Table 1
Demographics, treatment, and outcome in 31 pediatric patients with atypical teratoid rhabdoid tumors

Patient	Age* (y)	Location of tumor	Sequence of therapies	Delay to RT [†] (mo)	RT dose [‡] (Gy)	RT volume	Chemotherapy regimen	Pre-RT progression	Outcome
1	0.45	I	STR, PD ₁ , ChT ₁ , PD ₂ , STR ₂ , ChT ₂ , PD ₃ , STR ₃ , RT	21.0	50.4	Focal	CDDP/CYC/MTX/VP16	PD	DoD
2	0.53	S	GTR, ChT ₁ , RT, ChT ₂	6.5	54	Focal	CDDP/CYC/VCR	–	NED
3	0.55	I	STR, NTR, ChT, PD, RT	6.0	45	Focal	Dox/CDDP/IT-MTX/VCR	PD	DoD
4	0.61	I	GTR, ChT, PD ₁ , RT, PD ₂	6.2	55.8	Focal	IT-Maf/VCR/CYC/CDDP/VP16	PD	DoD
5	0.87	I	GTR, ChT, RT	7.8	50.4	Focal	Dox/CDDP/CYC/VCR	–	NED
6	0.98	S	GTR, ChT, RT	8.4	50.0	CSI	BCM	PD	DoD
7	1.05	I	GTR, ChT ₁ , PD, RT, ChT ₂	3.9	50.4	Focal	CDDP/CYC/VCR/VP16	PD	NED
8	1.19	I	GTR, ChT, RT	8.5	50.4	Focal	CDDP/VCR/CYC/IT-Maf/Bu/THIO	–	NED
9	1.28	S	STR ₁ , ChT, PD, STR ₂ , RT	5.7	54	CSI	IT-Maf/VCR/CYC/CDDP/VP16	PD	DoD
10	1.37	S	STR, ChT, RT	5.5	50.4	Focal	IT-Maf/VCR/CYC/CDDP/VP16	–	NED
11	1.61	I	STR, ChT ₁ , RT ₁ , PD, ChT ₂ , RT ₂	5.1	30.6	Focal	CDDP/CYC/VCR	–	AwD
12	1.76	S	GTR ₁ , ChT ₁ , PD ₁ , ChT ₂ , PD ₂ , GTR ₂ , RT	5.9	55.2	CSI	CDDP/VCR/CYC/VP16	PD	DoD
13	1.93	S	STR, ChT ₁ , RT, ChT ₂ , PD, ChT ₃	4.1	54	Focal	CDDP/CYC/VCR	–	AwD
14	2.16	I	GTR, ChT, PD, RT	5.2	54	CSI	CDDP/VCR/CYC/VP16/IT-Maf/Bu/THIO	PD	DoD
15	2.29	S	GTR, ChT, RT	4.2	50.4	Focal	BCM	–	NED
16	2.30	S	GTR, ChT ₁ , PD, RT, ChT ₂	3.6	54	Focal	CDDP/CYC/MTX/VP16	PD	DoD
17	2.36	I	STR, ChT, PD ₁ , RT, PD ₂	6.2	54	CSI	IT-Maf/VCR/CYC/CDDP/VP16	PD	DoD
18	2.50	I	STR ₁ , STR ₂ , PD, ChT, RT	1.8	52.2	Focal	ICE	PD	DoD
19	2.69	S	STR, ChT ₁ , PD ₁ , RT, ChT ₂ , PD ₂	6.5	55.8	CSI	IT-Maf/VCR/CYC/CDDP/VP16	PD	DoD
20	3.34	S	GTR, RT, ChT	0.6	55.8	CSI	CDDP/CYC/VCR	–	NED
21	3.64	S	STR ₁ , ChT ₁ , STR ₂ , RT, ChT ₂	2.4	55.8	CSI	CDDP/CYC/VCR	–	NED
22	3.67	S	GTR, RT, ChT	0.9	55.8	CSI	CDDP/CYC/VCR	–	NED
23	3.77	I	GTR, RT, ChT	0.7	55.8	CSI	CDDP/CYC/VCR	–	NED
24	3.90	S	GTR, RT, ChT ₁ , PD ₁ , ChT ₂ , PD ₂	0.6	55.8	CSI	CDDP/CYC/VCR	–	AwD
25	3.96	S	STR, ChT, PD, RT	7.0	66.6	CSI	ICE	PD	DoD
26	4.87	I	GTR, RT, ChT	1.0	55.8	CSI	CDDP/CYC/VCR	–	NED

Patient	Age* (y)	Location of tumor	Sequence of therapies	Delay to RT [†] (mo)	RT dose [‡] (Gy)	RT volume	Chemotherapy regimen	Pre-RT progression	Outcome
27	5.61	S	GTR, ChT, PD ₁ , RT, PD ₂	2.8	62.55	CSI	ICE	PD	DoD
28	7.33	S	STR, ChT ₁ , PD, RT, ChT ₂	2.5	55.8	CSI	CDDP/CYC/VCR	PD	DoD
29	9.89	I	GTR, PD ₁ , RT ₁ , ChT ₁ , PD ₂ , RT ₂ , ChT ₂ , PD ₃ , RT ₃	3.3	55.8	CSI	CYC/TOPO	PD	DoD
30	15.07	I	STR, NTR, RT, ChT ₁ , PD, ChT ₂	1.2	54	CSI	BCNU	PD	DoD
31	16.87	I	STR, RT ₁ , ChT, RT ₂	0.5	50.4	CSI	BCM	–	DoD

Abbreviations: AwD = alive with disease; IT-Maf = intrathecal mafosfamide; Bu = busulfan; THIO = thiotepa; BCM = best clinical management; BCNU = carmustine; DoD = dead of disease; CDDP = cisplatin; ChT = chemotherapy; CSI = craniospinal irradiation; CYC = cyclophosphamide; Dox = doxorubicin; GTR = gross total resection; I = infratentorial; ICE = ifosfamide, carboplatin, etoposide; MTX = methotrexate; NED = no evidence of disease; NTR = near-total resection; PD = progressive disease; – = no progression; RT = radiotherapy; S = supratentorial; STR = subtotal resection; TOPO = topotecan; VCR = vincristine; VP16 = etoposide.

*Data were obtained at the time of diagnosis.

[†]Data represent the period of time from diagnosis to initiation of radiotherapy.

[‡]Data represent the dose of radiotherapy delivered to the primary tumor site.

Table 2

Disease status at diagnosis and before radiotherapy for atypical teratoid rhabdoid tumors with time to progression vs. time to radiotherapy

Patient	At diagnosis		Immediately before RT		Time (mo)	
	Metastases	Surgical resection	Metastases	Tumor bed	Time to progression from diagnosis	Time to RT from diagnosis
1	+	STR	+	PD	1.1	21.0
2	-	GTR	-	NED	-	6.5
3	+	STR	+	PD	5.3	6.0
4	-	GTR	-	PD	5.5	6.2
5	+	GTR	-	NED	-	7.8
6	-	GTR	-	PD	14.7	8.4
7	+	GTR	-	PD	3.3	3.9
8	+	GTR	+	NED	-	8.5
9	-	STR	+	PD	4.7	5.7
10	-	STR	-	NED	-	5.5
11	-	STR	-	PD	12.1	5.1
12	-	GTR	-	PD	3.6	5.9
13	+	STR	-	NED	-	4.1
14	-	GTR	+	PD	0.9	5.2
15	-	GTR	-	NED	-	4.2
16	-	GTR	-	PD	3.1	3.6
17	+	STR	-	PD	5.7	6.2
18	+	STR	+	PD	1.3	1.8
19	-	STR	+	PD	5.9	6.5
20	-	GTR	-	NED	-	0.6
21	-	STR	-	NED	-	2.4
22	-	GTR	-	NED	-	0.9
23	-	GTR	-	NED	-	0.7
24	-	GTR	-	NED	-	0.6
25	-	STR	+	PD	3.1	7.0
26	-	GTR	-	NED	-	1.0
27	-	GTR	-	PD	5.8	2.8

At diagnosis			Immediately before RT		Time (mo)	
Patient	Metastases	Surgical resection	Metastases	Tumor bed	Time to progression from diagnosis	Time to RT from diagnosis
28	-	STR	+	PD	26.4	2.5
29	-	GTR	-	PD	2.4	3.3
30	+	STR	-	PD	14.7	1.2
31*	+	STR	+	PD	3.0	0.5

Abbreviations: GTR = gross total resection; NED = no evidence of disease; PD = progressive disease; RT = radiotherapy; STR = subtotal resection. Boldface reflects time to progression during chemotherapy, before radiotherapy.

* Infield metachronous atypical teratoid rhabdoid tumors developed 5 years after irradiation for Stage IIB Hodgkin lymphoma.

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Table 3

Cox regression model for progression-free survival

Clinical factor	Variable	Total (no. of events)	Model estimate (SE)	p value	Hazard ratio (95% CI)
Extent of resection	GTR vs. other	31 (21)	-0.59 (0.48)	0.02	0.55 (0.21–1.42)
	Months		0.12 (0.06)	0.05	1.13 (1.00–1.28)
Age at diagnosis	Years		0.08 (0.07)	0.21	1.09 (0.95–1.24)

Abbreviations: CI = confidence interval; RT = radiotherapy; SE = standard error.

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Table 4

Cox regression model for overall survival

Clinical factor	Variable	Total (no. of events)	Model estimate (SE)	p value	Hazard ratio (95% CI)
Disease progression before RT	Yes vs. no	31 (17)	-3.03 (1.07)	0.004	20.78 (2.58–167.60)
	Months		-0.03 (0.07)	0.74	0.98 (0.85–1.13)
Age at diagnosis	Years		-0.004 (0.07)	0.96	1.0 (0.87–1.15)

Abbreviations: CI = confidence interval; RT = radiotherapy; SE = standard error.

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Table 5

Cumulative incidence regression model for local treatment failure

Clinical factor	Variable	Coefficient	Standard error	p value	Hazard ratio (95% CI)
CSI	Yes vs. no	1.56	0.83	0.06	4.78 (0.94–24.36)
Extent of resection	GTR vs. other	−1.42	0.68	0.04	0.24 (0.06–0.91)
Time from diagnosis to RT	Months	0.20	0.08	0.007	1.23 (1.06–1.42)
Age at diagnosis	Years	0.08	0.07	0.26	1.08 (0.95–1.23)

Abbreviations: CI = confidence interval; CSI = craniospinal irradiation; GTR = gross total resection; RT = radiotherapy.