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ORIGINAL ARTICLE

Role of early and aggressive post-operative radiation therapy in improving outcome for pediatric central nervous system atypical teratoid/rhabdoid tumor

Wan-Chin Yang[1,2] · Hsiu-Ju Yen[2,3] · Muh-Lii Liang[2,4] · Hsin-Hung Chen[2,4] · Yi-Yen Lee[2,4] · Tai-Tong Wong[5] · Yu-Wen Hu[1,2] · Yi-Wei Chen[1,2]

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Abstract

Purpose The purpose of the study is to evaluate possible prognostic factors and optimal management for pediatric atypical teratoid/rhabdoid tumor (AT/RT) of the central nervous system (CNS).

Methods Twenty-eight pediatric patients with CNS AT/RT who were treated with radiation therapy (RT) as part of multimodality treatment regimens at a single institution (1996–2015) were reviewed. Survival outcomes were analyzed in relation to possible prognostic factors.

Results The 28 patients analyzed were followed up for a median 48-month period. Median progression-free survival (PFS) was 11 months, and overall survival (OS) was 57 months. Patients < 3 years old had RT delayed for a longer period after surgery ($p = 0.04$), and the mean RT dose to tumor bed was lower ($p < 0.01$) than in patients ≥ 3 years old. In multivariate analysis, a higher primary tumor bed RT dose was identified as a favorable prognostic factor for both PFS (hazard ratio [HR] = 0.85 per gray, $p < 0.01$) and OS (HR = 0.92 per gray, $p = 0.02$). In addition, an interval between surgery and RT initiation > 2 months, with disease progression observed before RT, as compared with an interval ≤ 2 months without disease progression prior to RT, was associated with worse PFS (HR = 8.50, $p < 0.01$) and OS (HR = 5.27, $p < 0.01$).

Conclusions Early and aggressive RT after surgery is critical for successful disease control in AT/RT patients. Conversely, a delay in RT until disease progression is observed that leads to unfavorable outcomes.

Keywords High-dose chemotherapy · Radiation dose · Radiation therapy · Time interval

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✉ Yi-Wei Chen
chenyw@vghtpe.gov.tw

[1] Division of Radiation Oncology, Department of Oncology, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Road, Beitou District, Taipei 112, Taiwan, Republic of China

[2] National Yang-Ming University School of Medicine, No. 155, Sec. 2, Linong Street, Taipei 112, Taiwan, Republic of China

[3] Division of Pediatric Hematology and Oncology, Department of Pediatrics, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Road, Beitou District, Taipei 112, Taiwan, Republic of China

[4] Division of Pediatric Neurosurgery, The Neurological Institute, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Road, Beitou District, Taipei 112, Taiwan, Republic of China

[5] Department of Neurosurgery, Taipei Medical University Hospital, Taipei Medical University, No. 252, Wuxing St., Xinyi District, Taipei 112, Taiwan, Republic of China

Introduction

Atypical teratoid/rhabdoid tumor (AT/RT) is a rare subtype of embryonal tumors that is characterized by a lack of INI-1 protein expression [4, 11, 15]. The age distribution of patients with AT/RT is younger than that characteristic of patients with medulloblastoma or embryonal tumors with multilayered rosettes [25]. Furthermore, the prognosis for AT/RT is worse than that for medulloblastoma [13], with a 20–40% metastatic rate at diagnosis [12, 14] and a median survival of 9–15 months [14, 25].

High heterogeneity has been observed among treatment protocols described in most studies of AT/RT [9, 12]. Consequently, no definitive conclusions have been drawn regarding prognostic factors and optimal treatment. Moreover, despite the young age distribution for AT/RT, which makes patients more susceptible to complications associated with aggressive treatment strategies, several studies have

demonstrated the necessity for intensive multimodality treatments [7, 10, 23, 24]. Accumulating evidence also suggests an important role for radiation therapy (RT) [1, 5, 10]. However, there is still no definitive consensus regarding the sequence of RT and chemotherapy, irradiation field, and RT dose that should be utilized [14].

In 2006, a review of 17 patients with AT/RT treated at Taipei Veterans General Hospital from 1990 to 2003 reported a median overall survival (OS) of 17 months in these patients [6]. In the present study, we included a larger number of patients and analyzed more detailed profiles. The aim of the present study was to identify patient characteristics and treatment factors that may influence treatment outcome for patients with AT/RT.

Methods

Patients and treatment

Pediatric AT/RT patients who received treatment at Taipei Veterans General Hospital between 1996 and 2015 were retrospectively reviewed. Only patients who received RT as part of their treatment were included in our analysis.

All patients underwent brain and spine magnetic resonance imaging (MRI) prior to or within 1 week after a craniotomy. A pathological diagnosis of AT/RT was made based on both histological features and negative immunohistochemical (IHC) staining for INI-1 [3, 15] after 2007. For those patients diagnosed before 2007, when the initial diagnosis was only based on histology, additional IHC staining was performed subsequently to confirm the diagnosis. The multimodality treatment included surgery, RT, and chemotherapy. Surgery was classified as gross total/nearly total resection, subtotal resection, or biopsy only, according to the surgeon's judgment during surgery and post-operative imaging results. RT was administered either immediately after surgery or after a few cycles of chemotherapy. For chemotherapy, the main regimens that were administered included intravenous administration of ifosfamide, cisplatin, and etoposide (ICE). From 2008, patients < 3 years of age have received a single or tandem high dose of chemotherapy, followed by autologous hematopoietic cell rescue (HDCT/AuHCR), in addition to conventional chemotherapy. The HDCT conditioning regimen includes carboplatin, thiotepa, and etoposide, or cyclophosphamide and melphalan.

Outcome measurement and statistical analysis

Characteristics and treatments of patients < 3 years old were compared with those ≥ 3 years old, using Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. OS, progression-free survival (PFS), and neuro-axis failure-free survival were analyzed using the Kaplan–Meier (K–M) method. OS was calculated from the date of diagnosis to the date of death from any cause. PFS was defined as the interval between the end of RT and the first evidence regarding relapse or progression at any site or death from any cause. Neuro-axis failure was defined as newly found seeding in the brain or spinal canal or progression of original seeding lesions. Neuro-axis failure-free survival was calculated from the end of RT to the date of the first evidence of neuro-axis failure or death from any cause.

Univariate Cox regression analyses were performed to identify potential prognostic factors for OS and PFS and to analyze the effect of CSI on neuro-axis failure-free survival. Factors with a p value ≤ 0.1 in the univariate Cox regression were further analyzed in a multivariate Cox regression analysis. For the analysis of OS, Cox regression with time-dependent covariates was applied to the treatment factors whose status could change over time, in order to eliminate a possible immortal time bias [21].

All of the analyses performed were two-sided, and the cut-off p value for significance was 0.05. For patients who were followed for more than 5 years, late sequelae were reported.

Results

Patients

Thirty patients were initially identified; however, two patients were excluded because they did not receive RT as a result of mortality soon after diagnosis. Thus, 28 patients were analyzed. The median age at diagnosis for this cohort was 4.3 years (range, 0.6–19.0 years). The baseline characteristics and treatment profiles are presented in Table 1. Details regarding the individual patients are presented in Supplementary Table 1. Twelve patients (42.9%) were < 3 years old. Primary tumors were localized to the infra-tentorial region ($n = 21$), supra-tentorial region ($n = 6$), and spinal canal ($n = 1$). Six patients (21.4%) exhibited image evidence of neuro-axis seeding at diagnosis. Cerebrospinal fluid cytology at diagnosis was available for 11 of 22 patients who had no evidence of seeding based on MRI, and all exhibited negative results. Gross total or nearly total tumor resection was achieved in 12 (42.9%) patients. None of the 28 patients had synchronous or metachronous rhaboid tumors outside of the CNS.

Radiation therapy

The median age of patients at the time of RT was 4.3 years (range, 1.0–19.1 years). A comparison of characteristics and treatments between the patients aged < 3 years versus ≥ 3 years is presented in Table 2. The median intervals between surgery and RT for the two age groups were 4.0 and 0.7 months,

Table 1 Patient characteristics

Characteristics	
Age at diagnosis, *N* (%)	
< 3 years	12 (42.9)
≥ 3 years	16 (57.1)
Median (years)	4.3
Gender, *N* (%)	
Male	16 (42.9)
Female	12 (57.1)
Tumor location, *N* (%)	
Supra-tentorial	6 (21.4)
Infra-tentorial	21 (75.0)
Spinal canal	1 (3.6)
Neuro-axis seeding at diagnosis	6 (21.4)
Surgery, *N* (%)	
Gross total/nearly total tumor resection	12 (42.9)
Partial tumor resection or biopsy only	16 (57.1)
Age at initiation of RT, *N* (%)	
< 3 years	11 (39.3)
≥ 3 years	17 (60.7)
Median age (years)	4.3
Interval between surgery and RT initiation, *N* (%)	
≤ 2 months	15 (53.6)
> 2 months	13 (46.4)
Evidence of disease progression after surgery and prior to RT initiation, *N* (%)	
Primary site failure only	5 (17.9)
New neuro-axis spreading only	4 (14.3)
Both	2 (7.1)
Radiation therapy volume, *N* (%)	
Focal irradiation only	8 (28.6)
Craniospinal irradiation + focal boost	20 (71.4)
Radiation therapy technique, *N* (%)	
2D	1 (3.5)
3D-conformal radiation therapy	25 (89.3)
Intensity modulation radiation therapy	2 (7.1)
Craniospinal irradiation dose (Gy)	
Mean (SD)	29.6 (3.1)
Range	24.0–36.0
Range of dose per fraction	1.5–1.8
Primary tumor bed RT dose (Gy)	
Mean (SD)	48.7 (6.5)
Range	30.0–56.0
Range of boost dose	1.5–2.0
Chemotherapy, *N* (%)	
Prior to the start of RT	14 (50.0)
Concurrent with RT	7 (25.0)
After RT	20 (71.4)
HDCT/AuHCR	8 (28.6)

RT radiation therapy, *HDCT/AuHCR* high-dose chemotherapy and autologous stem cell rescue, *SD* standard deviation

respectively ($p = 0.04$). Overall, 11 of 13 patients who received RT > 2 months after surgery experienced disease progression before RT was started. Among these 11 patients, 5 exhibited primary tumor relapse, 4 exhibited new neuro-axis seeding, and 2 exhibited both conditions. Moreover, 9 of these 11 patients were undergoing chemotherapy when disease progression was observed. The median time from surgery to disease progression was 3 months (range, 1–16 months).

Regarding RT volume, all of the patients ≥ 3 years old ($n = 16$) received CSI. Only 4 of 12 patients < 3 years old received CSI, while the remaining patients received focal irradiation to the primary tumor bed and seeding lesions. The mean CSI dose was 29.6 ± 3.1 gray (Gy), and the mean primary tumor bed dose was 48.7 ± 6.5 Gy. The RT details of individual patients are presented in Supplementary Table 2. The mean primary tumor bed dose used in patients < 3 years old was significantly lower than that used in patients ≥ 3 years old (46.1 ± 4.3 Gy vs. 50.6 ± 7.3 Gy, respectively; $p < 0.01$).

Chemotherapy

Twenty-four patients received chemotherapy. The chemotherapy was administered intravenously at three different time points: prior to the start of RT ($n = 14$), concurrent with RT ($n = 7$), or after RT ($n = 20$) (Table 1). In addition, seven of these patients underwent a ventricular lumbar infusion of nimustine (ACNU). Intrathecal (IT) chemotherapy was administered to three patients who were < 3 years old. HDCT/AuHCR was administered to eight patients (66.7%) who were < 3 years old (Table 2). RT was delayed until after HDCT/AuHCR for two patients; one exhibited disease progression after HDCT/AuHCR, while the other exhibited partial disease regression after HDCT/AuHCR.

Treatment outcomes

The median follow-up time for the entire cohort was 48 months (range 10–191 months). At the end of follow-up, 15 patients (53.6%) experienced disease relapse: two patients exhibited primary site failure, eight patients exhibited neuro-axis seeding, and five patients exhibited both conditions. The median PFS was 11 months, and the median OS was 57 months (Fig. 1a, b). The 3-year PFS and OS rates were 46.4 ± 9.4% and 57.1 ± 9.4%, respectively.

Univariate Cox regression analysis (Table 3) revealed that an interval between surgery and RT initiation of > 2 months (hazard ratio [HR], 3.38; 95% confidence interval [CI] 1.29–8.86; $p = 0.01$) and disease progression before RT initiation (HR, 3.28; 95% CI 1.28–8.38; $p = 0.01$) were both associated with worse PFS. Higher primary tumor bed RT dose (HR, 0.90 per Gy increase; 95% CI 0.84–0.97; $p < 0.01$) was associated with better PFS.

For OS, an interval between surgery and RT initiation of > 2 months (HR, 4.24; 95% CI 1.52–11.90; $p < 0.01$) was associated with worse OS. Worse OS with disease progression prior to RT initiation (HR, 2.53; 95% CI 0.96–6.64; $p = 0.06$) and better OS with higher primary tumor bed RT dose (HR, 0.94 per Gy increase; 95% CI 0.89–1.01; $p = 0.07$) exhibited borderline statistical significance. Kaplan–Meier plots are shown in Fig. 2a–f. Notably, the extent of resection did not significantly impact PFS or OS on univariate Cox analysis.

Due to possible interactions between the interval from surgery to RT initiation and disease progression rate prior to RT, a two-by-two combination of these two factors into four

Table 2 Comparison of characteristics and treatments between patients < 3 and ≥ 3 years old

	< 3 years old	≥ 3 years old	*p* value
Patient number, *N*	12	16	–
Median age at RT (year)	1.9	7.8	–
Neuro-axis spreading at diagnosis, *N* (%)	2 (16.7)	4 (25)	0.67
Median interval between surgery and RT initiation (month (IQR))	4.0 (0.6–16.2)	0.7 (0.4–7.0)	0.04
Interval between surgery and RT initiation > 2 months, *N* (%)	8 (66.7)	5 (31.2)	0.13
Disease progression prior to RT initiation, *N* (%)	7 (58.3)	3 (18.8)	0.02
Craniospinal irradiation, *N* (%)	4 (33.3)	16 (100.0)	< 0.01
Mean RT dose for primary tumor, (Gy (SD))	46.1 (4.3)	50.6 (7.3)	< 0.01
HDCT/AuHCR, *N* (%)	8 (66.7)	0 (0.0)	< 0.01

N number, *IQR* interquartile range, *SD* standard deviation, *RT* radiation therapy, *HDCT/AuHCR* high-dose chemotherapy and autologous stem cell rescue

covariates was included in a multivariate regression model (Table 4). Higher primary tumor bed RT dose was identified as a favorable prognostic factor for both PFS (HR, 0.85 per Gy increase; 95% CI 0.77–0.94; $p < 0.01$) and OS (HR, 0.92 per Gy increase; 95% CI 0.85–0.99; $p = 0.02$). In contrast, an interval between surgery and RT initiation of > 2 months, with disease progression observed before RT, was associated with worse PFS (HR, 8.50; 95% CI 2.39–30.19; $p < 0.01$) and worse OS (HR, 5.27; 95% CI 1.65–16.81; $p < 0.01$) than an interval ≤ 2 months without disease progression prior to RT. Unfortunately, the numbers of patients with an interval between surgery and RT initiation ≤ 2 months with disease progression, and with an interval between surgery and RT initiation > 2 months without disease progression, were too small for meaningful comparisons with the other two groups.

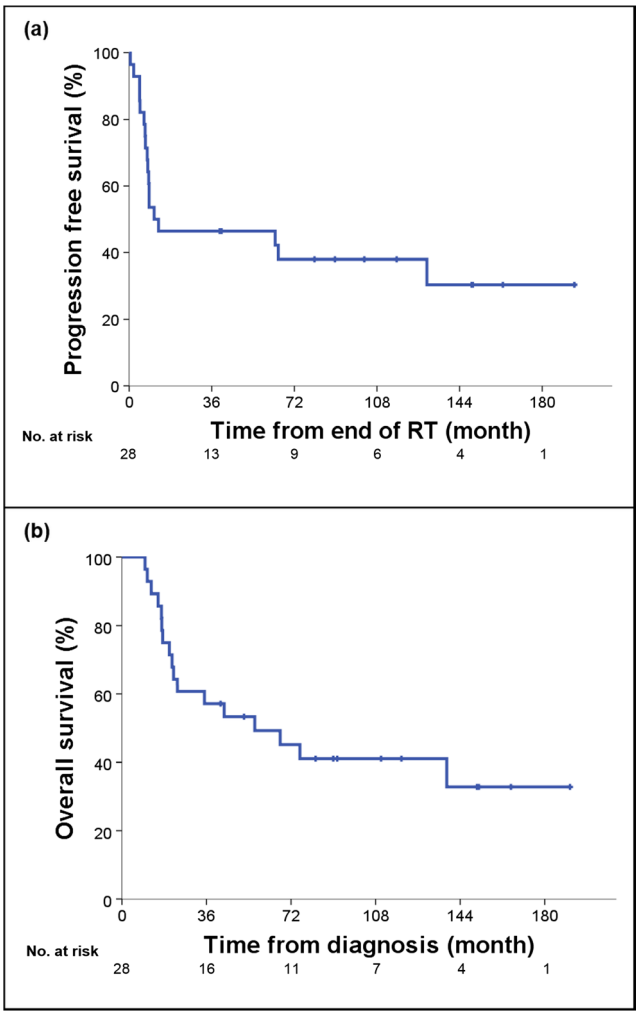

Fig. 1 Kaplan–Meier plot of **a** progression-free survival and **b** overall survival for the 28 patients studied

Among the eight patients who received focal irradiation without CSI, six patients exhibited neuro-axis failure after RT. In a univariate Cox analysis, CSI was associated with better neuro-axis failure-free survival (HR, 0.37; 95% CI 0.13–1.01; $p = 0.05$), with borderline statistical significance.

For patients < 3 years old, the median OS of the eight patients who underwent HDCT/AuHCR was 35 months (range, 17–90 months) and four survived for more than 3 years without evidence of disease. In contrast, three of the four patients who received IV ± IT chemotherapy alone died of their disease within 2 years.

Of the 15 patients who exhibited disease relapse or progression after RT, 14 (93.3%) experienced disease-related death, with 11 dying within 1 year after their disease relapse was detected.

Late sequelae in long-term survivors

There were 12 (42.9%) patients who were followed for more than 5 years, and all of them were disease free at the end of their follow-up. The most common sequelae for these patients were short stature ($n = 7$), muscle weakness ($n = 5$), neurocognitive development deficits ($n = 5$), and endocrine insufficiency ($n = 4$). One patient developed quadriparesis, and one had a vegetative status, and both eventually died of pneumonia. One patient developed hemiparesis, while four patients were ambulatory despite various degrees of limb

Table 3 Univariate Cox regression for progression-free survival and overall survival

Variables	Progression-free survival			Overall survival		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
≥ 3 vs. < 3 years[b]	0.58	0.22–1.51	0.26	0.69	0.25–1.86	0.46
Neuro-axis seeding at diagnosis						
Yes vs. no[b]	0.74	0.21–2.66	0.64	0.71	0.20–2.56	0.60
Extent of tumor resection						
GTR vs. STR/biopsy[b]	1.06	0.42–2.70	0.90	1.01	0.39–2.63	0.98
Interval between surgery and RT initiation						
> 2 vs. ≤ 2 months[b]	3.38	1.29–8.86	0.01	4.24[a]	1.52–11.90	< 0.01
Disease progression prior to RT initiation						
Yes vs. no[b]	3.28	1.28–8.38	0.01	2.53[a]	0.96–6.64	0.06
Craniospinal irradiation						
Yes vs. no[b]	0.42	0.15–1.16	0.10	0.65[a]	0.19–2.20	0.49
Primary tumor bed RT dose (per gray increase)	0.90	0.84–0.97	< 0.01	0.94	0.89–1.01	0.07
Chemotherapy						
Yes vs. no[b]	1.87	0.43–8.25	0.41	2.11[a]	0.48–9.33	0.33
HDCT/AuHCR						
Yes vs. no[b]	0.93	0.30–2.86	0.89	0.92[a]	0.29–2.89	0.89

HR hazard ratio, *95% CI* 95% confidence interval, *GTR* gross tumor resection, *STR* subtotal tumor resection, *RT* radiation therapy, *HDCT + AuHCR* high-dose chemotherapy and autologous stem cell rescue

[a] Cox regression with time-dependent covariate was used

[b] Reference

weakness. Academic performance was documented within medical records in nine of these patients: three required special education, and six attended regular school, but three of these six children had learning or social problems in school. Four patients required long-term hormone replacement for endocrine insufficiency, and two patients relied on antiepileptic drugs for seizure control. A secondary malignancy developed in three patients. The latter included a dural malignant spindle cell tumor, which developed 5 years after RT, a skull osteosarcoma, which developed 3 years after RT, and a glioblastoma, which developed 7 years after RT.

Discussion

The results of the present study demonstrated that, for the cohort examined, a high radiation dose for the primary tumor bed was associated with better PFS and OS. In contrast, a delay in RT for more than 2 months after surgery, with disease progression observed prior to RT, was associated with worse PFS and OS. Furthermore, 76.9% of the patients who received RT > 2 months after surgery experienced disease progression before RT, even though 81.8% of these patients were receiving chemotherapy when disease progression was observed. Similarly, in a German HIT database study, a 56% failure rate during initial post-operative chemotherapy was observed [25]. Thus, chemotherapy alone after surgery, without immediate RT, may not be adequate for treating AT/RT. Moreover, in a study conducted at St. Jude Hospital, a 23% increase in local failure was observed when RT was delayed ≥ 1 month after surgery [16]. However, to reduce the possible risk of late sequelae, RT is often deferred in young children [10, 16], or it serves as a salvage treatment. In the present study, the median interval between surgery and RT was longer, with a lower mean tumor bed RT dose, for patients < 3 years old than for older children. While these differences in treatment for the two age groups did not translate into significant differences in survival, possibly due to the small number of patients examined, the benefits and costs of postponing RT in young children should be carefully evaluated.

In the analysis of patients < 3 years old, half of those who underwent HDCT/AuHCR survived for more than 3 years without evidence of disease, but most of the patients who received IV ± IT chemotherapy alone died of disease within 2 years after diagnosis. In retrospective reviews of patients with AT/RT, a significant survival benefit has been associated with HDCT [10, 14, 17]. Based on this evidence, investigators have attempted to use HDCT/AuHCR to avoid, or defer, RT in young patients with AT/RT. A study from Vienna [20] reported a 100% 5-year OS in patients who received RT after

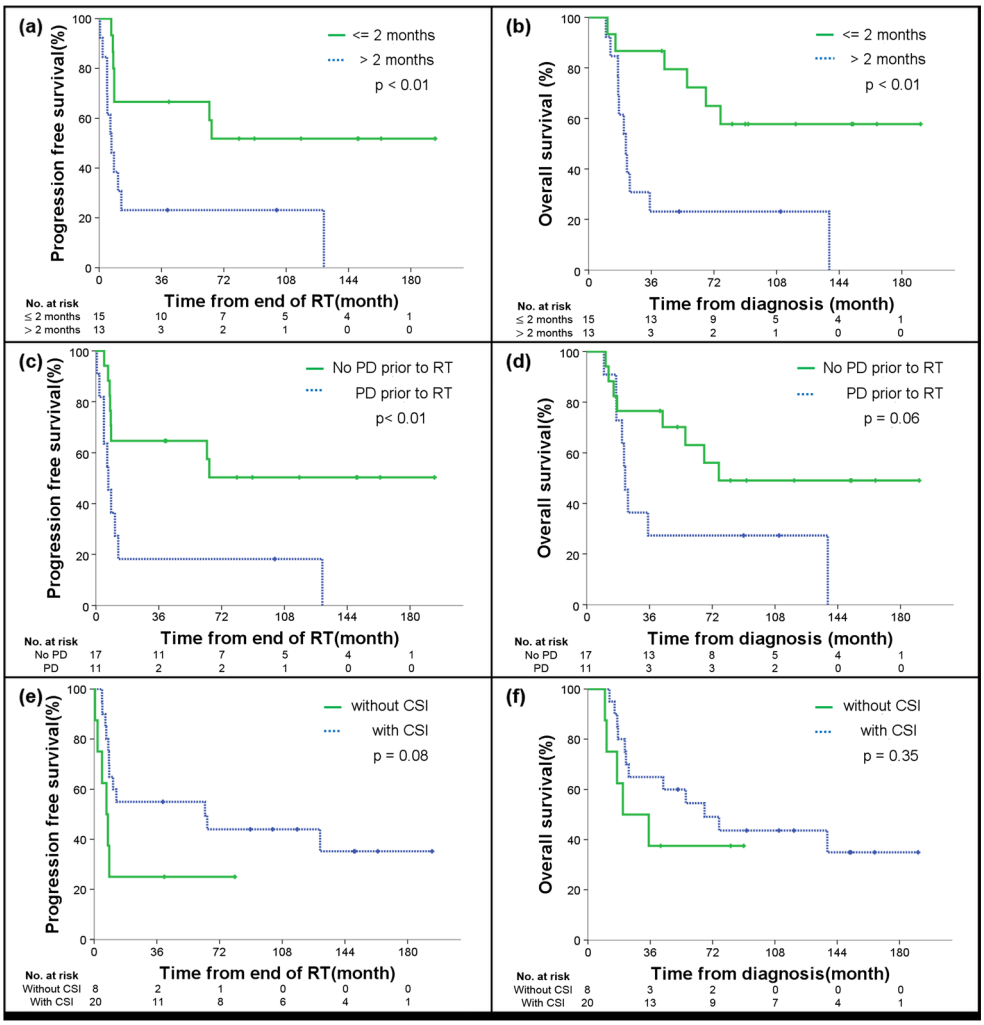

Fig. 2 Kaplan–Meier plots for progression-free survival (PFS) and overall survival (OS) according to different factors. **a** PFS: interval between surgery and radiotherapy (RT) initiation ≤ 2 and > 2 months. **b** OS: interval between surgery and RT initiation ≤ 2 and > 2 months. **c** PFS: without and with disease progression prior to RT initiation. **d** OS: without and with disease progression prior to RT initiation. **e** PFS: without and with craniospinal irradiation. **f** OS: without and with craniospinal irradiation. RT radiation therapy, PD progressive disease, CSI craniospinal irradiation

Table 4 Multivariate Cox regression for progression-free survival and overall survival

Variables	Progression-free survival			Overall survival		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Interval between surgery and RT initiation/disease progression prior to RT initiation[a]						
≤ 2 months/no[d]	1.00			1.00		
≤ 2 months/yes[b]	2.29	0.23–23.02	0.48	0.00	–	0.99
> 2 months/no[c]	2.52	0.45–14.11	0.29	3.95	0.74–21.08	0.11
> 2 months/yes	8.50	2.39–30.19	< 0.01	5.27	1.65–16.81	< 0.01
Craniospinal irradiation						
Yes vs. no[d]	0.69	0.21–2.26	0.54	–	–	–
Primary tumor bed RT dose (per gray increase)	0.85	0.77–0.94	< 0.01	0.92	0.85–0.99	0.02

HR hazard ratio, *95% CI* 95% confidence interval, *RT* radiation therapy

[a] Cox regression with time-dependent covariate was used

[b] The patient number of "≤ 2 months/yes" was only 1

[c] The patient number of "> 2 months/no" was only 3

[d] Reference

courses of chemotherapy and HDCT/AuHCR. However, other studies have reported less favorable results. Among 19 children treated with the Head Start III protocol, which involves intensive induction chemotherapy followed by HDCT/AuHCR, without early RT, 11 children experienced disease progression [26]. In a prospective Korean study, HDCT/AuHCR was performed to defer RT for patients with AT/RT, who were < 3 years old; all five of these patients eventually died of disease [22]. In the present cohort, RT was delayed by HDCT/AuHCR in two patients. In one of these patients, new seeding was observed after HDCT/AuHCR, while the other patient exhibited disease regression before RT was initiated. While this evidence suggests that HDCT/AuHCR may improve treatment outcome, trials need to be conducted to clarify the role of HDCT/AuHCR in delaying RT in young patients.

There is no definitive conclusion regarding the most appropriate irradiation volume for patients with AT/RT who are < 3 years old. In the present study group, univariate analysis identified an association between CSI and improved neuro-axis failure-free survival. While CSI is widely considered to be the primary treatment for patients ≥ 3 years old, focal irradiation is more often administered to young children to avoid complications that can arise following CSI [8, 18]. To date, a direct comparison of CSI efficacy and focal irradiation has not been published exclusively for patients with AT/RT. However, a few studies have reported that for patients treated with focal irradiation, with IT chemotherapy included in their treatment protocol, more than half of these patients were alive without evidence of disease at the end of their follow-up [7, 12, 20]. Therefore, IT chemotherapy may achieve better neuro-axis control when focal irradiation without CSI is administered.

The effect of the extent of resection on outcomes has been discussed in several publications [1, 2, 14, 16, 19], but the results were inconsistent across studies. In the current study, univariate analyses showed no statistically significant effects of this factor on PFS and OS. Further investigation is needed to establish the role of complete resection in the treatment of AT/RT.

There are limitations associated with the present study. First, due to rarity, the small number of patients examined was under-powered for drawing valid conclusions. Second, various RT and chemotherapy protocols were used in the cases of AT/RT examined, thereby introducing heterogeneity into our study population. Due to these limitations, further studies with a larger sample size and a well-designed treatment protocol are needed to confirm the reported results.

Conclusions

In conclusion, for patients with AT/RT, early and aggressive RT following surgery is essential for better disease control and improved survival. In younger patients, high-dose chemotherapy with autologous stem cell rescue may augment treatment efficacy, although it remains to be determined whether this treatment approach can be used to delay RT. It is anticipated that long-term survival will be achieved with improvements in treatment, although reducing and managing late toxicities caused by aggressive treatment is also of great importance.

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

Compliance with ethical standards

The study was conducted in accordance with the Declaration of Helsinki.

Ethical approval The data of this study was extracted from database of pediatric brain tumors in Taipei Veterans General Hospital, and the study protocol was approved by the Institutional Review Board of the Taipei Veterans General Hospital. The IRB number is 97-07-05A.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent to this study was obtained from the parents of all participants.

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