Atypical Teratoid/Rhabdoid Tumor in Taiwan

Subjects: Oncology | Pediatrics

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Atypical teratoid/rhabdoid tumor (AT/RT) is a rare, highly aggressive embryonal brain tumor most commonly presenting in young children. Older age, supratentorial site, and treatment with radiotherapy, chemotherapy, or both were significantly associated with better survival of patients with AT/RT in Taiwan.

atypical teratoid/rhabdoid tumor | CNS tumors | pediatric cancer | survival outcome

1. Introduction

Atypical teratoid/rhabdoid tumor (AT/RT) is a rare and highly malignant cancer of the central nervous system (CNS). AT/RT represents 1 to 2% of all pediatric CNS tumors [1][2][3][4] and is the most common CNS malignant tumor in children under 3 years of age [1][5]. In children under the age of 1, AT/RT accounts for 40 to 50% of CNS malignancies [2]. It is more prevalent in males and in children of European descent [6][7]. AT/RT is characterized by loss-of-function alterations in the *SMARCB1* gene on chromosome 22q11.2 in more than 95% of patients, with the remainder having mutations in *SMARCA4*, located on chromosome 19p13.2 [2][8][9][10]. AT/RTs have been found throughout the CNS, most commonly in the infratentorial region; their location may vary with age [2][11].

Pathologically, AT/RTs are embryonal tumors that have a rhabdoid morphology, as well as areas with primitive neuroectodermal, mesenchymal, and epithelial features [5]. Radiographically, AT/RT typically presents as a large, heterogeneous mass with varying degrees of necrosis, hemorrhage, and peritumoral edema, mostly within the CNS but sometimes along the cranial nerves or at the skull base [2].

AT/RTs are highly malignant in nature and are classified as Grade IV CNS tumors according to the World Health Organization (WHO) classification [12]. Even with intensive multimodality therapies, the prognosis of AT/RT is poor, with a 15–53% of survival rate at three years and a median survival of approximately 1 year [3][8][13][14]. Due to the rare occurrence of AT/RT, the optimal treatment has yet to be determined, and therapeutic approaches vary from institution to institution [1][13]. AT/RTs are most commonly managed using a multimodality treatment that includes surgery followed by chemotherapy, radiotherapy, high-dose chemotherapy with stem cell therapy (SCT), and intrathecal or intraventricular (IT/IVent) chemotherapy [2]. Although the extent of surgical resection has been proven to be associated with better outcomes, there is no universally accepted chemotherapy or radiotherapy regimen for AT/RT. Previous studies suggest that patients may have a longer disease-free survival with SCT [5]. To reduce the risk of neurocognitive toxicity in younger patients, radiotherapy may be delayed; however, this may affect the overall survival [2][15].

2. Current Insights

2.1. Demographic and Clinical Characteristics

The demographic and clinical characteristics of the study population are shown in **Table 1**. Of 47 enrolled patients with AT/RT, 29 were male (61.70%). The mean age of the patients was 66.87 (±109.32) months; 11 patients were younger than 12 months of age (23.40%), 15 were 12 to 35 months old (31.91%), and 21 were 36 months of age or older (44.68%). Regarding the tumor site, 46.81% of the tumors were in the infratentorial region or in the spine (*n* = 22), 29.79% were at an unspecified site (*n* = 14), and 23.40% were in the supratentorial region (*n* = 11). In this group, 24 patients received combined radiotherapy and chemotherapy (51.06%), 12 patients received chemotherapy only (25.53%), 6 patients received surgery only or no treatment (12.77%), and 5 patients received radiotherapy only (10.64%). In addition, 24 patients were diagnosed between 1999 and 2007 (51.06%), and 23 patients were diagnosed between 2008 and 2014 (48.94%). Nearly half of the patients (*n* = 21, 44.68%) were from Northern Taiwan, followed by Central Taiwan (*n* = 15, 31.91%) and then Southern Taiwan (*n* = 11, 23.40%).

Table 1. Demographic and clinical characteristics of the patients.

Variables	Total (*N* = 47) *
Mean age at diagnosis (months) * Median age at diagnosis (months)	66.87 (±109.32) 23.3 (12.5–87.9)
Age group (months)	
0–11 months	11 (23.40%)
12–35 months	15 (31.91%)
≥36 months	21 (44.68%)
Gender, Male	29 (61.70%)
Residence Location	
Northern Taiwan	21 (44.68%)
Central Taiwan	15 (31.91%)
Southern Taiwan	11 (23.40%)
Tumor site	
Supratentorial	11 (23.40%)
Infratentorial or Spine	22 (46.81%)
Unspecified nervous system or Others	14 (29.79%)

Variables	Total (*N* = 47) *
Treatment	
Surgery or no treatment	6 (12.77%)
Chemotherapy (including SCT)	12 (25.53%)
RT	5 (10.64%)
RT + CT	24 (51.06%)
Diagnosis year	
2008–2014	23 (48.94%)
1999–2007	24 (51.06%)

* Variables are expressed as mean ± standard deviation (SD) or median (interquartile range (IQR)) for continuous data, and *n* (%) for categorical data.

2.2. Distribution of Tumor Site and Treatment across Age Groups

In **Table 2**, which compares the tumor site and treatment across age groups, we noted a trend of a higher prevalence of infratentorial/spinal tumors in younger patients (*n* = 15) and of supratentorial tumors in older patients (*n* = 8) (*p* = 0.082). Children younger than 3 years of age more commonly had surgery only or no treatment (*n* = 6 and 0), and fewer received treatment with chemotherapy and/or radiotherapy than children 3 years or older (*n* = 20 and 21) (*p* = 0.026).

Table 2. Comparison of tumor site and treatment types for different age groups.

Tumor Site	Age < 3 Years (*N* = 26)	Age ≥ 3 Years (*N* = 21)	Total (*N* = 47)	*p* Value
Supratentorial	3 (27%)	8 (73%)	11	0.082 [a]
Infratentorial or Spine	15 (68%)	7 (32)	22	
Unspecified nervous system or Others	8 (57%)	6 (43%)	14	
Treatment	**(*N* = 26)**	**(*N* = 21)**	**(*N* = 47)**	
Chemotherapy and/or radiotherapy	20 (49%)	21 (51%)	41	0.026 [b]
Surgery or No treatment	6 (100%)	0 (0%)	6	

[a] Chi-square test of independence; [b] Fisher's exact test.

We found no significant relationship between tumor site and treatment (**Table 3**; *p* = 0.6588).

Table 3. Comparison of tumor site for different treatment types.

Tumor Site	Chemotherapy Only (*N* = 12)	Radiotherapy with/without Chemotherapy (*N* = 29)	Surgery or No Treatment (*N* = 6)	Total (*N* = 47)	*p* Value *
Infratentorial or Spine	7 (32%)	12 (54%)	3 (14%)	22	0.698
Supratentorial, Unspecified or Others	5 (20%)	17 (68%)	3 (12%)	25	

* Fisher's exact test.

2.3. Prognostic Factors

Kaplan–Meier analysis (**Figure 1**) showed that the survival probabilities of the patients who were aged ≥36 months (**Figure 1**a), whose tumor was located at a supratentorial site (**Figure 1**d), and who received radiotherapy (**Figure 1**e), were significantly higher (all $p < 0.05$ by log-rank test) than those of the other patients. Gender, residence location in Taiwan, and diagnosis year had no significant influence on survival (**Figure 1**b,c,f; all $p > 0.05$ by log-rank test). When analyzing survival, we found that all infants with AT/RT diagnosed at age <12 months (n = 11 (23%)) died within 18 months from diagnosis, while cases diagnosed at ages 12–35 months (n = 15 (32%)) had a 5-year overall survival probability (5y-OS) of 28%, and those diagnosed at the age of ≥36 months (n = 21 (45%)) had a 5y-OS of 41% ($p < 0.0001$). All cases treated with surgery only (n = 6 (13%)) died within 6 months; all cases treated with chemotherapy without radiotherapy (n = 12 (25%)) died within 3 years; all cases treated with radiotherapy only (n = 5 (11%)) had a 5y-OS of 60%; the other cases treated with radiotherapy and chemotherapy (n = 24 (51%)) had a 5y-OS of 42.22% ($p < 0.0001$). Patients with a supratentorial tumor (n = 11 (23%)) had a 5y-OS of 51.95%, those with an unspecified nervous system tumor (n = 14 (30%)) had a 5y-OS of 21.43%, and those with an infratentorial or spine tumor (n = 22 (47%)) had a 5y-OS of 17.36% ($p < 0.05$).

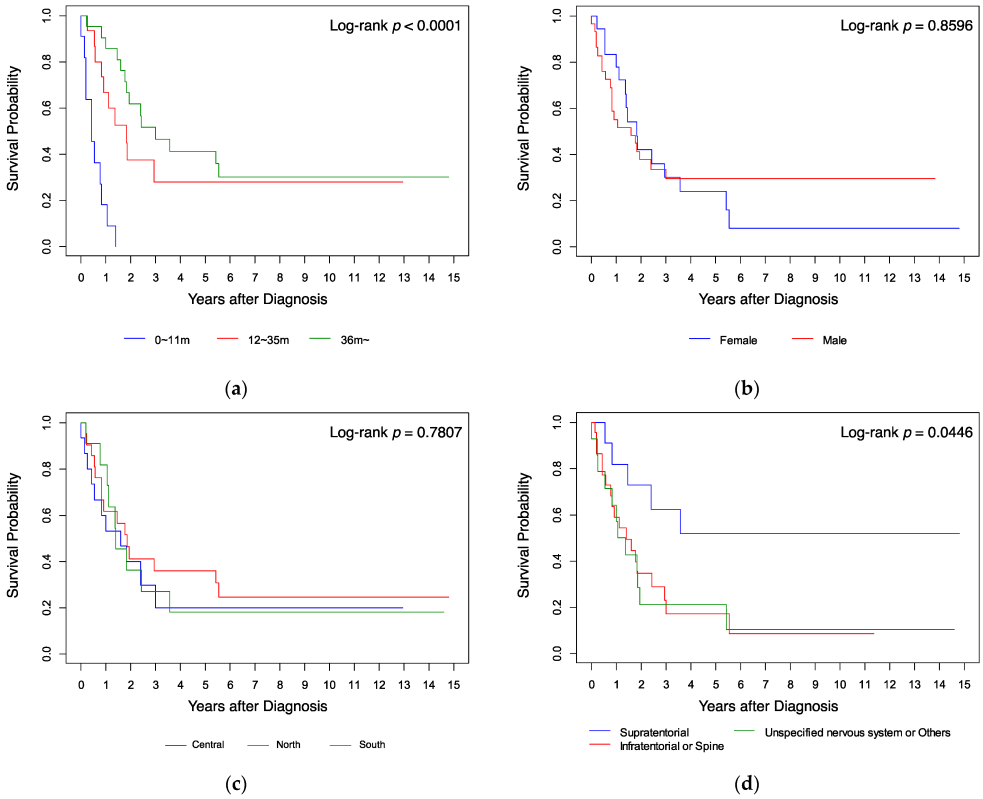

Figure 1. Kaplan–Meier analysis of survival curves compared by (**a**) age, (**b**) gender, (**c**) resident location, (**d**) tumor site, (**e**) treatment, and (**f**) diagnosis year.

Table 4 shows the results of univariate and multivariate analyses of factors that affect survival. Compared to the age group 0–11 months as a reference, the age groups 12–23 months (HR 0.113, 96% CI 0.039–0.330) and ≥36 months (HR 0.078, 95% CI 0.028–0.216) had a better prognosis on univariate analysis (both $p < 0.001$). On multivariate analysis, the 12–23 months group had a better prognosis (HR 0.130, 95% CI 0.036–0.468; $p = 0.002$). Compared to supratentorial tumors, tumors in the infratentorial or spine regions and tumors in an unspecified location of the nervous system or other location had a poorer prognosis in both univariate (HR 3.121, 95% CI 1.146–8.497; $p = 0.026$ and HR 3.261, 95% CI 1.139–9.337; $p = 0.028$ respectively) and multivariate analyses (HR 3.234, 95% CI 1.049–9.973; $p = 0.041$ and HR 3.505, 95% CI 1.121–10.955; $p = 0.031$). On univariate analysis, chemotherapy (including SCT) (HR 0.079, 95% CI 0.021–0.305; $p < 0.001$), radiotherapy (HR 0.011, 95% CI 0.002–0.063; $p < 0.001$), and combined radiotherapy and chemotherapy (HR 0.016, 95% CI 0.004–0.066; $p < 0.001$) were associated with better outcome. On multivariate analysis, chemotherapy (HR 0.013, 95% CI 0.002–0.097), radiotherapy (HR 0.002, 95% CI 0.000–0.025), and combined radiotherapy and chemotherapy (HR 0.003, 95% CI 0.000–0.031) remained significant protective prognostic factors (all $p < 0.001$). Gender and diagnosis year were not significant prognostic factors on either univariate or multivariate analysis.

Table 4. Univariate and multivariate analyses of factors affecting outcome.

Prognostic Factor	Univariate			Multivariate		
	HR	95% CI	*p* Value *	HR	95% CI	*p* Value *
Age (months)						
0–11 m		Reference			Reference	
12–23 m	0.113	(0.039–0.330)	**<0.001**	0.130	(0.036–0.468)	**0.002**
24–35 m	0.379	(0.082–1.754)	0.214	1.769	(0.175–17.852)	0.629
≥36 m	0.078	(0.028–0.216)	**<0.001**	0.356	(0.066–1.929)	0.231
Gender						
Female		Reference			Reference	
Male	0.942	(0.481–1.844)	0.862	1.012	(0.430–2.379)	0.979
Tumor site						
Supratentorial		Reference			Reference	
Infratentorial or Spine	3.121	(1.146–8.497)	**0.026**	3.234	(1.049–9.973)	**0.041**
Unspecified nervous system or Others	3.261	(1.139–9.337)	**0.028**	3.505	(1.121–10.955)	**0.031**
Treatment						
Surgery or No treatment		Reference			Reference	
Chemotherapy (including SCT)	0.079	(0.021–0.305)	**<0.001**	0.013	(0.002–0.097)	**<0.001**
Radiotherapy	0.011	(0.002–0.063)	**<0.001**	0.002	(0.000–0.025)	**<0.001**
Radiotherapy + Chemotherapy	0.016	(0.004–0.066)	**<0.001**	0.003	(0.000–0.031)	**<0.001**
Diagnosis year						
1999–2007		Reference			Reference	
2008–2014	1.439	(0.725–	0.298	1.316	(0.477–3.632)	0.596

Prognostic Factor	Univariate			Multivariate		
	HR	95% CI	*p* Value *	HR	95% CI	*p* Value *
		2.856)				

* *p* values < 0.05 are presented in bold.

3. Conclusions

Since AT/RT is a rare disease, it is not easy for a single center to follow many patients longitudinally. The Taiwan Cancer Registry, a nationwide, population-based database, is therefore a useful resource for monitoring and analyzing the clinical characteristics and the treatment outcomes of AT/RT. It's found that patients at an older age at diagnosis and those with supratentorial tumors had a better prognosis. These data also support the effectiveness of radiotherapy, chemotherapy, or combined radiotherapy and chemotherapy. These data can inform future radiotherapy and chemotherapy regimens, clinical trial design, and risk stratification for AT/RT.

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