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CLINICAL INVESTIGATION

Radiation Therapy Plays an Important Role in the Treatment of Atypical Teratoid/Rhabdoid Tumors: Analysis of the EU-RHAB Cohorts and Their Precursors

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Purpose: Atypical teratoid/rhabdoid tumor (AT/RT) is a rare malignancy of the central nervous system in young children with a dismal prognosis. Prognostic markers have been extensively investigated but have not been validated. The role of radiation therapy (RT) remains controversial. We evaluated the impact of RT as part of multimodality treatment by analyzing data of a European AT/RT cohort.

Methods and Materials: We retrospectively analyzed data of the European Registry for Rhabdoid Tumors and its precursors. Primary endpoints were progression-free survival (PFS) and overall survival (OS). Potential impact of prognostic factors was analyzed using univariable and multivariable Cox regression analyses with RT as a time-dependent factor.

Results: Data of 186 children (118 male, 68 female) treated from 1990 to 2016 were evaluable. The median age at diagnosis was 1.57 years (range, 0.01-26.70 years); 47% (87/186) of the patients were under the age of 18 months. Sixty-nine percent (128/186) received RT (focal RT, n = 93; craniospinal treatment with local boost, n = 34; spinal irradiation, n = 1). The median

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Data Sharing Statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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follow-up duration of the entire cohort was 1.73 years (range, 0.06-20.11 years). The estimated PFS and OS rates were 48% (95% CI, 41%-55%) and 72% (95% CI, 65%-78%) at 1 year and 33% (95% CI, 26%-40%) and 49% (95% CI, 41%-56%) at 2 years, respectively. On multivariable analysis, RT was an independent significant prognostic factor for PFS (hazard ratio, 0.45; 95% CI, 0.27-0.75; $P = .002$) and OS (hazard ratio, 0.54; 95% CI, 0.32-0.93; $P = .025$).

Conclusions: This analysis confirms the relevance of local therapies. RT was an independent prognostic factor for outcomes in children experiencing AT/RT. However, long-term sequelae have to be carefully evaluated and considered given the young age at time of RT.

Introduction

Atypical teratoid/ rhabdoid tumor (AT/RT) is a rare embryonal tumor of the central nervous system (CNS) that typically develops during early childhood,[1-3] with the median age at diagnosis ranging from 12 to 24 months.[2,4,5] Up to one-third of patients have metastatic disease at diagnosis.[2,6-8] Even with contemporary trimodality treatment, AT/RT is associated with a dismal prognosis, with median survival ranging from 10 to 20 months[1,2,4] and 5-year overall survival (OS) from 28% to 34%.[3,4,6-8]

The strongest independent prognostic factor is age at diagnosis, with very young age associated with inferior outcomes.[2,4,6,9-11] Whereas maximal resection and high-dose chemotherapy are associated with improved outcomes, metastatic disease at diagnosis appears to be a negative prognostic factor.[1,2,4,7-9,11-13] The role of radiation therapy (RT) remains controversial. Previous studies have indicated that the use of RT is beneficial for OS,[14-16] even in infants and very young children.[1,17,18] Current evaluations of large cohorts in population-based studies also indicate that RT has positive effects[2,4] but not a survival benefit.[12] Due to the risk of severe late complications from treatment,[14] ideal treatment strategies in very young children remain a matter of investigation. The current analysis aimed to examine the role of RT in a large European cohort over a long treatment period.

Methods and Materials

We retrospectively reviewed the data of patients with AT/RT registered in the European Registry for Rhabdoid Tumors (EU-RHAB)[19] or its pilot RHABDOID 2007. In addition, the data of patients with AT/RT mainly treated in Germany and Austria before the initiation of the EU-RHAB and enrolled in observational arms of the HIT/HIT-SKK and AT/RT-ZNS studies of German children, toddlers, and infants with brain tumors were included in the analysis. Treatment was provided according to each study's respective guidelines, which represented the consensus of treatment standards for AT/RT. The chemotherapy strategies used have been previously described.[9,20,21]

According to EU-RHAB and HIT/HIT-SKK concepts, RT was provided to children ranging from 1.5 to 3.0 years except in high-risk scenarios.[22-24] The EU-RHAB recommends early local RT after surgery for localized disease of a total dose of 54.0 Gy and consideration of a boost up to 59.4 Gy for residual disease.[22] For treatment of local disease, focal RT was recommended. For treatment of metastatic disease, craniospinal irradiation (CSI) was recommended with dose to the entire craniospinal axis of 35.2 Gy in patients ≥3 years and 24.0 Gy in patients 18 months to 3 years. The primary tumor site was to be boosted up to a total dose of 55.0 Gy and 54.6, respectively. For treatment of residual disease, an additional boost up to 59.4 Gy can be considered. For focal RT, the margin for the clinical target volume was typically 10 mm. Planning target volume margins followed institutional standards. Patients were selected for RT according to age, respective protocol, and individual treatment decisions.

Data were collected and updated from the EU-RHAB Radiation Therapy Reference Center and HIT and the EU-RHAB Trial Center. All legal guardian(s) gave informed consent for registration in the respective databases and analyses. This retrospective evaluation obtained approval from the Ethics Committee of the University Duisburg-Essen (16-6924-BO). The cohort was evaluated for clinical characteristics, tumor attributes, therapy details, and follow-up information. The extent of initial or second-look surgery, if performed, was considered resection status.

Statistical analysis

The χ^2 test was used to detect differences between the characteristics of the patients who received RT (the RT group) and the patients who did not receive RT (the non-RT group). Progression-free survival (PFS) and OS were the primary endpoints. PFS was calculated as the time from diagnosis, considered the date of first magnetic resonance imaging (MRI) or first surgery until first disease progression, or until relapse, considered the date of MRI with conspicuous finding, or death of any cause. Pattern of failure was defined as local when progression or relapse occurred at the primary tumor site and as disseminated when 1 or more new metastases occurred at a distant site not in contact to the primary tumor site, regardless of RT target volume. OS was defined as the time from diagnosis until death of any cause. PFS and OS were censored at the date of last contact. Kaplan-Meier estimates were used to calculate survival curves with 95% CIs.

The potential impact of prognostic factors on PFS and OS was analyzed by applying univariable and multivariable Cox regression. RT was considered a time-dependent

covariate. Other covariates were the extent of surgical resection, age at diagnosis (< or ≥18 months according to EU-RHAB RT recommendations[22]), sex, and presence of metastases. In a second multivariable Cox model, only patients who received RT as a first-line therapy were analyzed to avoid potential bias from patients who received RT after progressive disease (PD).

In subgroup analyses, only patients who received RT during first-line therapy and after PD were evaluated. In univariable analyses, outcomes were compared using the log rank test. Outcomes of patients treated with RT within first-line therapy were compared with the outcomes of patients treated with RT after PD. Additionally, we compared outcome of children with very young age at RT (<18 months).

In further subgroup analyses, we evaluated the outcomes of receiving below and above the current standard dose of 54 Gy (with a tolerance of 1.8 Gy). For analyzing outcome, we considered only patients who received RT within first-line therapy. The last subgroup analysis evaluated outcomes after focal irradiation or CSI at the M0 or M+ stage, excluding patients with missing data for M stage.

All statistical analyses were exploratory and not confirmatory. *P* values ≤.05 without adjustment for multiple testing were considered significant. An overall significance level was not determined and could not be calculated. All statistical analyses were performed using IBM SPSS version 20.7 and R version 4.1.2 software.

Results

Of the 203 children treated from 1990 to 2016 who had data available, 14 patients were excluded due to missing information and 3 due to lack of confirmation of diagnosis by histopathology. The final sample consisted of 186 patients, 118 male and 68 female, who had been treated for AT/RT between 1990 and 2016. For 45 patients (24%), data on SMARCB1 germline mutation were available. Among these 45 patients, 7 presented with a germline pathogenic variant of the SMARCB1 gene. Three patients (2%) had synchronous malignant rhabdoid tumor of the kidney. Ninety-five (51%) were treated according to the protocols of the EU-RHAB/RHABDOID 2007 study, 83 (45%) were treated according to the protocols of the HIT-/AT/RT-ZNS study, and 8 (4%) received individualized treatment. Patients were referred from 12 European countries, with the majority (n = 167; 90%) from Germany.

The median age at diagnosis was 1.57 years (range, 0.01-26.70 years). At initial diagnosis, 138 patients (74%) were younger than 3 years. Details on patient characteristics are presented in Table 1. Metastatic disease staging according to Chang et al[25] was available for 173 patients (93%), of whom 130 were staged as M0, 17 as M1, 6 as M2, 17 as M3, and 3 as M4. All but 1 patient underwent surgery, with 164 patients (88%) receiving total or subtotal surgery and 49 patients (26%) undergoing a second-look resection. In 10 patients (5%), information on the extent of resection was missing. In 146 patients (78%), date of surgery, including date of biopsy, was considered as date of initial diagnosis for analysis. For the 40 patients (22%) for whom date of surgery was missing, date of first MRI was considered as date of initial diagnosis, with a median time of 8 days between first MRI and surgery. Patients treated with RT were older compared with patients treated without RT, and the M stage differed between the groups.

Radiation therapy

Of the 128 patients (69%) who received RT in their therapy course, 104 (81%) received RT within first-line therapy and 24 (19%) after PD (Table 2). The median age at initial diagnosis and beginning of RT was 2.17 years (range, 0.01-26.70 years) and 2.79 years (range, 0.07-26.97 years), respectively. At the start of RT, 14 patients were younger than 18 months, of whom 4 were younger than 12 months. The median interval between diagnosis and initiation of irradiation was 0.35 years (range, 0.03-1.69 years) for patients irradiated during first-line therapy and 0.76 years (range, 0.27-2.41 years) for patients irradiated after PD. RT was provided after a median time interval of 0.64 years (range, 0.06-1.69 years) in patients younger than 18 months at diagnosis (n = 40) and after a median of 0.33 years (range, 0.03-2.41 years) in patients older than 18 months (n = 88). The median age at the beginning of CSI treatment was 3.88 years (range, 0.87-17.68 years). Fifteen patients were younger than three years. CSI was provided to 16 patients with M0 stage and 15 patients with M+ stage. As part of first-line therapy (n = 104), 78 and 25 patients received focal RT or CSI, respectively. One patient was irradiated only to the spinal CNS.

Outcomes of the entire cohort

The median and mean follow-up duration of the entire cohort was 1.73 and 3.31 years (range, 0.06-20.11 years), respectively. During the observation period, 122 patients (66%) experienced recurrent or progressive disease. The pattern of failure was either local (n = 80) or disseminated with or without local failure (n = 42). Estimated from the Kaplan-Meier curve, the median PFS for the entire cohort was 0.96 years (95% CI, 0.75-1.16 years; Fig. 1). The estimated 1-year and 2-year PFS rates were 48% (95% CI, 41%-55%) and 33% (95% CI, 26%-40%), respectively.

Of the 186 patients, 115 (62%) died. The causes of death were disease progression (n = 114) and secondary malignancy (n = 1). The estimated median OS of the entire cohort was 1.95 years (95% CI, 1.33-2.57 years; Fig. 1). The estimated 1-year and 2-year OS rates were 72% (95% CI, 65%-78%) and 49% (95% CI, 41%-56%), respectively. The median PFS and OS of patients treated according to the EU-RHAB/RHABDOID 2007 protocol (n = 95) was 1.1 years (95% CI, 0.5-1.7 years) and 2.7 years (95% CI, 1.0-4.4 years), respectively (Fig. E1A, B). The outcomes of the patients

Table 1 Demographic, clinical, and treatment characteristics of pediatric patients with atypical teratoid/rhabdoid tumors

Characteristic		Total (N = 186) No. patients (%)	RT group (n = 128) No. patients (%)	RT group, first line (n = 104) No. patients (%)	RT group, after PD (n = 24) No. patients (%)	Non-RT group (n = 58) No. patients (%)	P*
Sex	Male	118 (63.4)	84 (65.6)	65 (62.5)	19 (79.2)	34 (58.6)	.358
	Female	68 (36.6)	44 (34.4)	39 (37.5)	5 (20.8)	24 (41.4)	
Age at diagnosis	<18 mo	87 (46.8)	40 (31.3)	28 (26.9)	12 (50.0)	47 (81.0)	<.001
	≥18 mo	99 (53.2)	88 (68.8)	76 (73.1)	12 (50.0)	11 (19.0)	
Location	Supratentorial	87 (46.8)	67 (52.3)	54 (51.9)	13 (54.2)	20† (34.5)	.078
	Infratentorial	80 (43.0)	48 (37.5)	37 (35.6)	11 (45.8)	32 (55.2)	
	Bifocal	13 (7.0)	10 (7.8)	10 (9.6)		3 (5.2)	
	Spinal	5 (2.7)	2 (1.6)	2 (1.9)		3 (5.2)	
	NS	1 (0.5)	1 (0.8)	1 (1.0)			
Metastases at diagnosis	M0	130 (69.9)	96 (75.0)	79 (76.0)	17 (70.8)	34 (58.6)	.006
	M1-M4	43 (23.1)	22 (17.2)	16 (15.4)	6 (25.0)	21 (36.2)	
	NS	13 (7.0)	10 (7.8)	9 (8.6)	1 (4.2)	3 (5.2)	
Resection	Gross total	54 (29.0)	39 (30.5)	29 (27.9)	7 (29.2)	15 (25.9)	.957
	Subtotal	110 (59.1)	78 (60.9)	60 (57.7)	17 (70.8)	32 (55.2)	
	Biopsy only	11 (5.9)	5 (3.9)	9 (8.7)		6 (10.3)	
	NS	10 (5.9)	6 (4.7)	6 (5.8)		4 (6.9)	
	No resection	1 (0.5)				1 (1.7)	
Chemotherapy	Yes	178 (95.7)	125 (97.7)	101 (97.1)	24 (100)	53 (91.4)	.134
	No	6 (3.2)	2 (1.6)	2 (1.9)		4 (6.9)	
	NS	2 (1.1)	1 (0.8)	1 (1.0)		1 (1.7)	

Abbreviations: NS = not specified; PD = progressive disease; RT = radiation therapy.

* Comparison of RT group with non-RT group using the χ^2 test.

† Three patients with synchronous tumor of the kidney.

Table 2 Demographics and treatment parameters of patients who received radiation therapy

Parameter		All patients with RT (N = 128) No. patients (%)	RT group, first line (n = 104) No. patients (%)	RT group, after PD (n = 24) No. patients (%)
Age at RT	<18 mo	14 (10.9)	11 (10.6)	3 (12.5)
	≥18 mo	114 (89.1)	93 (89.4)	21 (87.5)
Volume	Focal	93 (72.7)	78 (75.0)	15 (62.5)
	CSI with local boost	34 (26.6)	25 (24.0)	9 (37.5)
	Spinal without local boost	1 (0.8)	1 (1.0)	
Technique	Photons	97 (75.8)	74 (71.2)	23 (95.8)
	Protons	25 (19.5)	25 (24.0)	1 (4.2)
	Photons/protons	1 (0.8)	1 (1.0)	
	NS	5 (3.9)	4 (3.8)	
Median total dose (Gy)	Focal	54.0 (20.0-71.0)	54.0 (20.0-71.0)	54.0 (44.5-59.4)
	CSI/spinal	35.2 (17.6-48.6)	35.2 (23.4-48.6)	24.0 (17.6-35.2)
Median fraction dose (Gy)		1.8 (1.0-4.0)	1.8 (1.0-4.0)	1.8 (1.5-3.0)

Abbreviations: CSI = craniospinal irradiation; NS = not specified; PD = progressive disease; RT = radiation therapy.

treated according to the EU-RHAB/RHABDOID 2007 protocol were superior compared with those of patients treated according to the HIT/ATRT-ZNS protocol (n = 83), for whom the median PFS and OS were 0.8 years (95% CI, 0.6-1.0 years) and 1.4 years (95% CI, 0.8-2.0 years), respectively (log rank; PFS: $P = .026$, OS: $P = .017$).

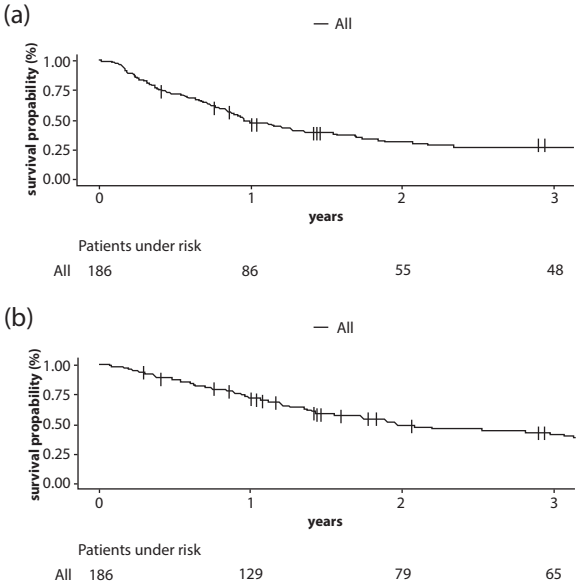

Fig. 1. Kaplan-Meier plots of outcomes of the entire cohort. (A) Progression-free survival. The estimated 1-year and 2-year progression-free survival rates were 48% (95% CI, 41%-55%) and 33% (95% CI, 26%-40%), respectively. (B) Overall survival. The estimated 1-year and 2-year overall survival rates were 72% (95% CI, 65%-78%) and 49% (95% CI, 41%-56%), respectively.

Outcomes of RT within first-line therapy

Between 1990 and 2016, 104 patients received RT within first-line therapy. PD was observed in 51 patients, of whom 27 had local and 24 had dissemination/combined (local plus dissemination). One patient, who received chemotherapy, developed acute myeloid leukemia 2.53 years after RT. In total, 48 patients who received RT died, all due to disease. Between 1993 and 2014, 58 patients were treated with therapy other than RT. Of the 47 patients who experienced recurrent/progressive disease, 33 experienced local and 14 dissemination/combined. In total, 51 patients died due to disease. Figure 2A and B display the Kaplan-Meier curves of PFS and OS for the RT and non-RT groups.

Prognostic factors

On univariable Cox analysis of the entire cohort, RT, extent of surgery, aged ≥ 18 months at initial diagnosis, and absence of metastasis were significant prognostic factors for improved PFS and OS (Table 3). On multivariable Cox regression, RT, extent of surgery, and aged ≥ 18 months remained independent significant prognostic factors for PFS and OS (Table 3).

We excluded the 24 patients who received RT after PD for a second Cox model. The results are displayed in Table 4.

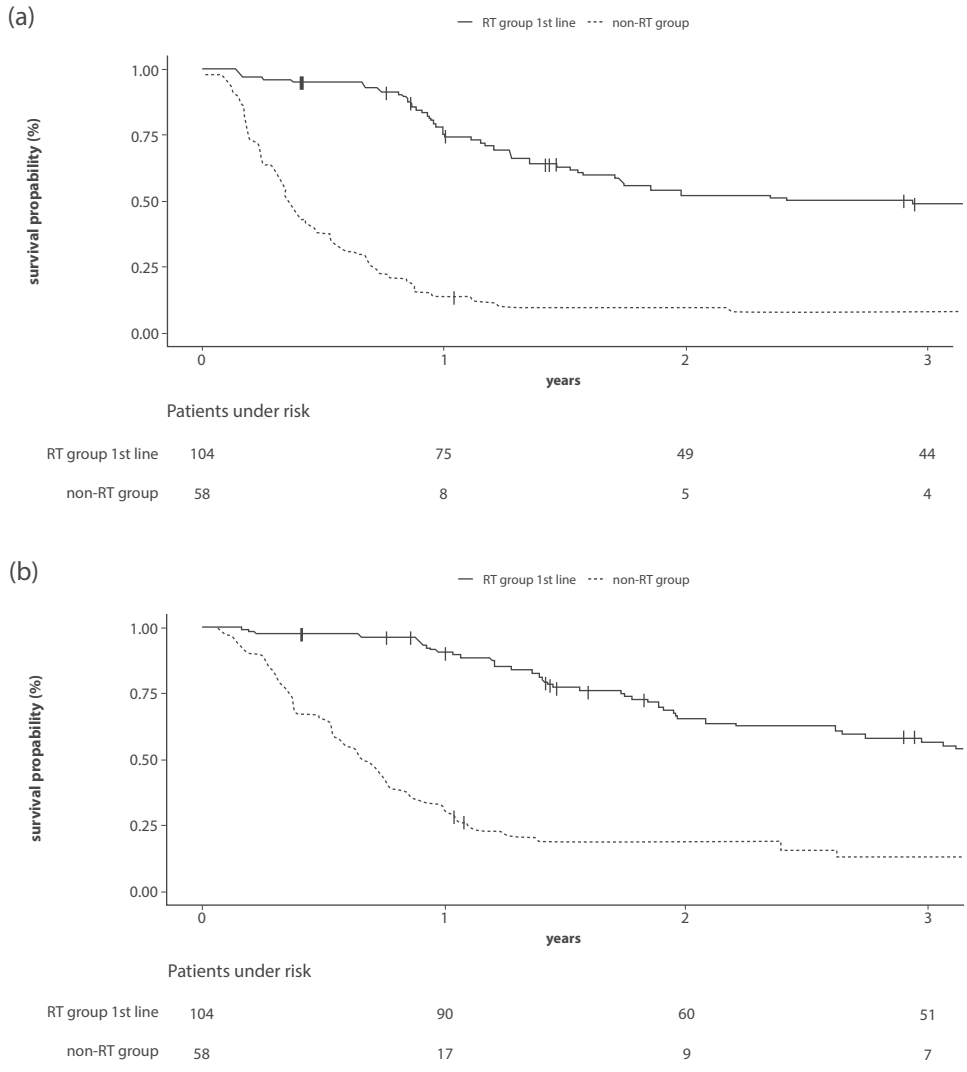

Fig. 2. Kaplan-Meier plot of outcomes of patients who received radiation therapy (RT) as first-line therapy. (A) Progression-free survival (PFS). The estimated 1-year and 2-year PFS rates of the RT group were 75% (95% CI, 67%-84%) and 52% (95% CI, 43%-63%), respectively. The estimated 1-year and 2-year PFS rates of the non-RT group were 14% (95% CI, 7%-26%) and 10% (95% CI, 4%-22%), respectively. (B) Overall survival (OS). The estimated 1-year and 2-year OS rates of the RT group were 90% (95% CI, 84%-96%) and 65% (95% CI, 56%-75%), respectively. The estimated 1-year and 2-year OS rates of the non-RT group after 1 and 2 years were 30% (95% CI, 20%-45%) and 18% (95% CI, 10%-32%), respectively.

Subgroup analyses

The first subgroup analysis included all 128 patients who had received RT. The median OS of the 104 patients irradiated during first-line therapy was 6.04 years (range, 0.61-20.1 years) and of the 24 patients irradiated after PD was 2.53 years (range, 0.8-11.6 years) (Fig. 3). Univariable analysis revealed borderline significance of improved OS for patients irradiated during first-line therapy compared with patients who were irradiated after PD ($P = .054$). Of the 128 patients, 14 were younger than 18 months (median, 12 months) when treated with RT. Of these 14 patients, 11 were treated during first-line therapy and 3 at PD after systemic therapy. All 3 patients irradiated at PD died due to disease 2, 6, and 9 months after RT. Of the 11 patients treated with RT during first-line therapy, 8 experienced PD after a median 0.6 years (range, 0.09-2.7 years), and 7 eventually died due to disease after a median 1.1 years (range, 0.13-3.12 years).

Further subgroup analyses evaluated dose thresholds below and above the current standard of 54 Gy. We excluded 3 patients receiving <40 Gy. The survival plot of the patients treated with RT within first-line therapy is displayed in Figure E2A and B. Additional subgroup analyses evaluated the subgroup of patients who received ≥54 Gy (Fig. E3A, B). Both analyses of dose thresholds showed no differences between the respective dose groups. The last subgroup analysis evaluated M stage and RT volume for treatment with focal RT and CSI, respectively, in patients who had received RT within first-line therapy. In the 78 patients

Table 3 Univariable and multivariable Cox regression analyses (with radiation therapy as a time-dependent covariate) of progression-free survival and overall survival of 186 patients with atypical teratoid/rhabdoid tumors

	Progression-free survival				Overall survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Radiation therapy								
No	Reference group		Reference group	.002	Reference group		Reference group	.025
Yes	0.41 (0.27-0.63)	<.001	0.45 (0.27-0.75)		0.47 (0.30-0.73)	<.001	0.54 (0.32-0.93)	
Resection								
Biopsy only	Reference group		Reference group	.015	Reference group		Reference group	.004
Subtotal	0.49 (0.25-0.95)	.033	0.43 (0.22-0.85)	.001	0.38 (0.19-0.77)	.007	0.35 (0.17-0.71)	< .001
Gross total	0.28 (0.14-0.58)	< .001	0.29 (0.13-0.61)		0.20 (0.09-0.43)	<.001	0.19 (0.08-0.42)	
Age category								
≥18 mo	Reference group	< .001	Reference group	.011	Reference group	< .001	Reference group	.008
<18 mo	2.12 (1.50-2.99)		1.67 (1.12-2.47)		2.21 (1.52-3.20)		1.79 (1.17-2.73)	
Sex								
Female	Reference group	.754	Reference group	.979	Reference group	.474	Reference group	.999
Male	0.95 (0.66-1.35)		1.01 (0.69-1.47)		0.87 (0.60-1.27)		1.00 (0.67-1.50)	
Metastases								
M+ (M1-M4)	Reference group	.013	Reference group	.306	Reference group	.008	Reference group	.130
M0	0.61 (0.41-0.90)		0.80 (0.52-1.23)		0.57 (0.38-0.86)		0.71 (0.46-1.11)	

Abbreviation: HR = hazard ratio.

Table 4 Univariable and multivariable cox regression analyses (with radiation therapy as a time-dependent covariate) of progression-free survival and overall survival of 162 patients with atypical teratoid/rhabdoid tumor in first-line therapy

	Progression-free survival				Overall survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Radiation therapy								
No	Reference group	.006	Reference group	.115	Reference group	<.001	Reference group	< .001
Yes	0.51 (0.32-0.82)		0.62 (0.35-1.12)		0.35 (0.22-0.55)		0.35 (0.19-0.62)	
Resection								
Biopsy only	Reference group		Reference group		Reference group		Reference group	
Subtotal	0.42 (0.22-0.82)	.011	0.40 (0.20-0.79)	.009	0.42 (0.21-0.85)	.016	0.36 (0.18-0.75)	.006
Gross total	0.23 (0.11-0.48)	< .001	0.27 (0.12-0.59)	.001	0.19 (0.08-0.41)	<.001	0.15 (0.07-0.36)	< .001
Age category								
≥18 mo	Reference group	< .001	Reference group	.007	Reference group	<.001	Reference group	.099
<18 mo	2.24 (1.53-3.29)		1.88 (1.19-2.97)		2.24 (1.50-3.34)		1.50 (0.59-1.40)	
Sex								
Female	Reference group	.469	Reference group	.736	Reference group	.385	Reference group	.658
Male	0.87 (0.59-1.27)		0.93 (0.61-1.42)		0.84 (0.56-1.25)		0.91 (0.59-1.40)	
Metastases								
M+ (M1-M4)	Reference group	.007	Reference group	.163	Reference group	.018	Reference group	.377
M0	0.55 (0.36-0.85)		0.71 (0.44-1.15)		0.58 (0.37-0.91)		0.80 (0.50-1.30)	

Abbreviations: HR = hazard ratio.

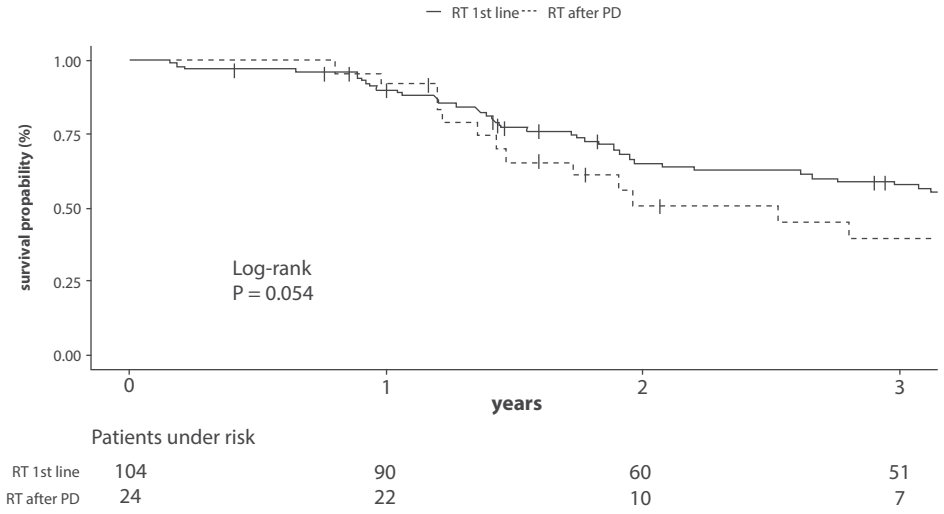

Fig. 3. Subgroup analysis. Kaplan-Meier plot of overall survival in patients with radiation therapy in their therapy course by time point of radiation therapy (within first-line therapy vs after progressive disease).

with stage M0 disease, 67 received focal RT, and 11 received CSI. PD was observed in 29 patients (43%) after focal RT and in 7 (64%) after CSI. Of these 36 patients, 27 (40%) died after focal RT treatment and 7 (64%) after CSI. Their survival plots show no significant differences between the groups (Fig. E4A, B). Of the 16 patients with M+ disease, 5 and 11 patients received focal RT and CSI, respectively (Fig. E5A, B). After focal RT, 2 patients developed PD and subsequently died, and 6 patients developed PD after CSI and all eventually died.

Discussion

This retrospective analysis of a European cohort confirms that receipt of RT is a significant prognostic factor for outcomes in children with AT/RT. Our results illustrate the overall unsatisfactory prognosis of this aggressive malignancy despite receipt of intensive treatment.

Cohort

Pooling the data of EU-RHAB and its precursors enabled us to build a large cohort (n = 186), including a considerable number of irradiated patients (69%) over a long treatment period (1990 and 2016). This absolute cohort size is comparable with those of Surveillance, Epidemiology, and End Results (SEER) publications that analyzed the data of 174 to 190 children with AT/RT.[1,2,13] One of the largest series (n = 361) contained RT treatment data for only 40% of the patients.[4] In the recent National Cancer Database analysis of 354 children under 3 years, 33% received RT.[26] Other previous analyses included a significantly lower number of patients reporting institutional experiences, prospective trials, or observational studies.[7,9,18,27-32]

Overall outcomes

The median OS of our cohort was poor, being only 1.95 years (23.4 months). An analysis of the U.S. SEER data collected between 2000 and 2015 showed similarly disappointing median OS durations, ranging from 20 to 24 months.[2] Previous data from the National Cancer Database of patients treated between 2004 and 2012 showed an even worse median OS of 14.3 months.[4] However, our data showed better outcomes with treatment using modern concepts (ie, the EURHAB/RHABDOID 2007 protocol) compared with historical schemes (ie, the HIT/ATRT-ZNS scheme), and suggest that overall treatment has improved over time.

RT as a prognostic factor

We found that extent of resection and age ≥18 months were independent prognostic factors for PFS and OS in the multivariable model. Our findings are in accordance with those of previous population-based studies; registry evaluations; and pooled data analyses showing a prolonged OS associated with age >1-3 years[2,4,6,9-11] and gross total resection.[7-9,12] RT has previously been examined as a prognostic factor, but mostly within smaller cohorts compared with ours and in studies using inhomogeneous treatment regimens or that use different methods of assessing survivorship.[1,2,8,9] A recent EU-RHAB evaluation of prognostic factors demonstrated a negative effect of omission of RT in univariate but not multivariable analysis.[6] Whereas the EU-RHAB study analyzed the data of 93 patients older than 1 year, we analyzed data of 186 patients of all age groups.

Role of RT in treatment of infants and toddlers

RT is usually avoided in very young children. However, a SEER analysis of 190 patients with AT/RT focusing on the effect of contemporary trimodality treatment showed superior survival with therapy that includes RT compared with surgery and chemotherapy alone.[2] Remarkably, infants and toddlers benefited the most from RT.[2] Other studies have demonstrated the positive role of RT in the treatment of very young children.[7,26,33] In accordance with these studies, our results confirm that the relevance of RT in AT/RT treatment is independent of age. However, the use of RT in childhood remains controversial due to potential late sequelae, particularly endocrine and neurologic impairments.[34] Unfortunately, long-term toxicity data were not available for the cohort we studied. Further research is necessary to investigate sequelae of this vulnerable group.

Proton beam therapy (PBT) is increasingly being used as a promising, sparing technique that may avoid the side effects attributed to other treatments.[28,29,35,36] In this analysis, however, only 19% of the irradiated patients received PBT, as the treatment period that we analyzed started in 1990, when PBT was rarely offered in Europe. The availability of PBT has significantly increased over the past decades[37,38] now allowing access to treatment with PBT for many children with AT/RT. Jazmati et al showed that PBT in children younger than 2 years was feasible and had acceptable toxicity during the first year(s) after treatment.[36] In localized ependymoma, immediate postoperative focal RT upon age 12 months is considered standard treatment.[39] In accordance, the current SIOP Ependymoma II trial (NCT02265770) established a minimum age of 12 months for RT.[40] The same cutoff is used in the current European multinational umbrella trial for patients with AT/RT (SIOPE ATRT 01, EudraCT Number: 2018-003335-29). It is hoped that this European study will provide more data concerning RT in AT/RT patients in the near future.

RT within first-line therapy compared with salvage RT

In young children, RT is typically postponed to reduce late effects. However, the early progressions observed may not only have been caused by the aggressiveness of AT/RT but also by the delay of RT. The aforementioned SEER analysis showed substantial benefit for OS when RT is part of first-line therapy, especially in young (≤3 years) children.[1] The prospective CCG-9921 study analyzed only patients under 3 years with malignant brain tumors, including AT/RT. Patients with PD who received RT had a 1.5-fold lower risk of death compared with children who did not receive RT after progression.[41]

Our results accord with these findings. In the comparison of the outcomes of patients irradiated during first-line therapy and the outcomes of patients irradiated after PD, the former showed borderline significantly improved OS. The results of our second Cox model with patients only irradiated during first-line therapy revealed a significantly positive effect of RT on OS, suggesting that "preventive" RT may be preferred over salvage RT, at least in older children.

Timing of RT

The optimal timing of RT as part of initial therapy remains under study. The prospective ACNS0333 study including 65 patients with AT/RT showed that the timing of RT (early vs postconsolidation) did not affect survival adversely even though postconsolidation RT administration was provided to very young patients (6-12 months) and patients with metastatic disease, both considered high-risk populations.[18] Although we did not study the sequencing within initial therapy in detail, we analyzed aforementioned timing of RT (preventive vs RT after PD). The cutoff for RT with regard to age was similar in all treatment strategies in our cohort while allowing for individual treatment decisions. In accordance with our data, the results of the ACNS0333 study showed that RT was feasible in children aged <6 to 12 months.[18] Nevertheless, the outcomes of our cohort of 14 children aged <1.5 years who received RT were poor, reflecting the high-risk profile of these very young patients. However, due to the small cohort size, we could not draw any conclusions for this subgroup.

Recurrence patterns

Because RT is a local treatment, recurrence patterns (local vs disseminated) are of particular importance. We found that 50% of the patients treated with RT within first-line therapy experienced local or combined failure after RT. Earlier reports showed higher rates of local and combined failure.[6,18,42] Nevertheless, RT remains an important part of local therapy that affects OS.

Subgroup analyses

Subgroup analysis of treatment fields displayed no differences in PFS and OS after focal irradiation or CSI. However, the sizes of the subgroups were very inhomogeneous. Our results support the European strategy of delivering CSI only to patients with metastatic disease (in patients aged ≥3 years).[22] Japanese data also indicated that patients with M0/M1 disease did not benefit from CSI.[43] In contrast, a recent report of the St. Jude trials showed that children ≥3 years of age with M0 disease benefited from postoperative CSI and adjuvant chemotherapy.[42] The use of CSI with regard to metastatic stage remains under investigation.

Subgroup analyses of dose thresholds did not indicate any effect of dose levels below or above the current standard of 54 Gy. However, due to the small number of patients whom we analyzed, the results must be interpreted with caution. The data may still support the ACNS0333 trial,

which proposes a lower dose of 50.4 Gy to the primary site in patients with AT/RT aged <36 months.[18] For residual disease, the current European protocol SIOP ATRT01 suggests an optional boost up to 59.4 Gy. Unfortunately, we were not able to provide evidence for use of this strategy, also due to small numbers of patients. However, it is promising that we achieved similar survival rates for patients who received 59.4 Gy and patients who received 54 Gy, bearing in mind that residual disease was proven to have negative effects on survival.

Limitations

This analysis contains several limitations. Selection bias may have had a significant effect on the benefits of RT. The treatment regimens were inhomogeneous regarding chemotherapy, RT doses, and fractionation schemes. Additionally, different photon and proton techniques were used, and treatment planning techniques have changed over time. It is now evident that apart from using modern techniques, assuring the quality of RT is of high importance. Inadequate application of RT can have a significantly negative effect on outcomes.[44] A recent report revealed a high rate of protocol deviations with regard to RT planning in children with medulloblastoma.[45] Use of pretreatment RT quality assurance programs are strongly recommended for future clinical trials. To date, RT quality control has been a missing aspect in AT/RT trials.

Another limitation was that some information on relevant parameters was missing. Data on late toxicity and second primary cancer were not available or incomplete. Future analyses must evaluate these crucial aspects. It would also be interesting to assess particular parameters of modern RT techniques and chemotherapy, such as high-dose RT, intrathecal chemotherapy, and treatment using other substances, to better understand optimal strategies and potential confounding factors. Molecular subgroups of AT/RT have been revealed and are suspected to influence treatment response[6,46] but were not available for our analysis. Future research must validate the effects of these subgroups on RT.

Conclusion

RT plays an important role in the treatment of AT/RT. However, long-term radiation-induced toxicity must be considered to better define the role of RT in very young children. Outcomes after use of contemporary RT techniques must be analyzed within prospective studies. At the same time, RT quality reviews must become integral parts of all clinical studies. Future protocols will reveal the efficacy of innovative treatment strategies.

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