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Radiotherapy plays an important role in the treatment of atypical teratoid/rhabdoid tumors – analysis of the EU-RHAB cohorts and their precursors

Role of radiotherapy in AT/RT

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Introduction

Atypical teratoid/ rhabdoid tumor (AT/RT) is a rare embryonal tumor of the central nervous system, which typically occurs during early childhood[1-3]. The median age at diagnosis ranges

between 12-24 months[2,4,5]. Up to one-third of patients suffer from metastatic disease at diagnosis[2,6-8]. In spite of contemporary trimodality treatment, AT/RT is associated with a dismal prognosis. The median survival time is 10-20 months[1,2,4]. Five-year overall survival (OS) is 28-34%[3,4,6-8].

The best-known independent prognostic factor is age at diagnosis. Very young age is associated with inferior outcomes[2,4,6,9-11]. Additionally, maximal resection and high-dose chemotherapy are associated with improved outcome, whereas metastatic disease at diagnosis appears to be a negative prognostic factor[1,2,4,7-9,11-13]. The role of RT remains controversial. There have been previous suggestions 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 of population-based studies also indicate a positive impact of RT[2,4]. In contrast, others do not show a survival benefit for RT[12]. Due to its risk for potential severe late complications[14], ideal treatment strategies in very young children are still a matter of investigation.

The current analysis aims to examine the role of RT in a large European cohort over a long treatment period.

Methods and Materials

We retrospectively reviewed data of patients with AT/RT registered in the European Registry for rhabdoid tumors (EU-RHAB)[19] or its pilot RHABDOID 2007. In addition, data of patients with AT/RT mainly treated in Germany and Austria before the initiation of the EU-RHAB registry, and enrolled in observational arms of studies for German children, toddlers, and infants with brain tumors HIT/HIT-SKK and AT/RT-ZNS, were included in the analysis. Treatment followed the respective guidelines, which represented the consensus of treatment standard for AT/RT. Information with regard to applied chemotherapy strategies were already described[9,20,21]. Within EU-RHAB and HIT/HIT-SKK concepts, RT was given in children older than 1.5-3.0 years, except in high-risk scenarios[22-24]. EU-RHAB recommended early

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local RT after surgery in localized disease with a total dose of 54.0 Gy, and consideration of a boost up to 59.4 Gy in residual disease[22]. In local disease, focal RT was recommended. In metastatic disease, craniospinal irradiation (CSI) was recommended with dose to the entire craniospinal axis of 35.2 Gy (in patients ≥ 3 years of age) and 24.0 Gy (in patients > 18 months < 3 years), respectively. The primary tumor site was to be boosted up to a total dose of 55.0 Gy and 54.6, respectively. In 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 were recommended to institutional standards. Patients were selected for RT according to age and respective protocol as well as according to individual treatment decisions.

Data was collected and updated from the reference center for RT of EU-RHAB and HIT as well as the EU-RHAB trial center. All legal guardian(s) gave informed consent for registering for 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 as resection status.

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Statistical analysis

Chi-squared test was used to detect differences of characteristics in the RT group and non-RT group. Progression-free survival (PFS) and OS were primary endpoints. PFS was calculated as the time from diagnosis (date of first magnetic resonance imaging (MRI) or first surgery) until first disease progression or relapse (date of MRI with conspicuous finding) or death of any cause. Pattern of failure was defined as local when progression or relapse occurred at primary tumor site, and as disseminated when one or more new metastases occurred at a distant site, not in contact to the primary tumor site, regardless of the 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. We used Kaplan-Meier estimates to calculate survival curves. 95% confidence intervals (CI) were given. Potential impact of prognostic factors on PFS and OS was analyzed applying univariable and multivariable Cox regression. RT was time-dependent covariate. Further covariates were the extent of surgical resection, age at diagnosis (</≥ 18 months according to EU-RHAB RT recommendations[22]), gender, and presence of metastases. In a second multivariable Cox model, we analyzed only patients with RT in first line strategy to avoid potential bias from patients with RT after progression disease (PD).

In subgroup analyses, we only considered patients who received RT (during first line therapy and after PD). In univariable analyses, outcome was compared using log rank tests. First, outcome in patients treated RT within first line therapy vs. RT after PD were evaluated. Additionally, we compared outcome of children with very young age at RT (< 18 months).
In further subgroup analyses, we evaluated impact below and above the current standard dose of 54 Gy (with a tolerance of 1.8 Gy). For analyzing outcome, we considered only patients RT within first line therapy. The last subgroup analysis evaluated outcome after focal irradiation or CSI at M0 or M+ stages. Patients with missing M-stage were excluded for this analysis.

All statistical analyses are exploratory, not confirmatory. P-values are regarded noticeable ("significant") in case $p \leq 0.05$ without adjustment for multiple testing. An overall significance level was not determined and cannot be calculated. We performed statistical analyses with IBM SPSS Statistics 20.7 (IBM Corp., Armonk, NY, USA) and R statistic software version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

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Initially data of 203 children treated from 1990-2016 were available; however seventeen patients were excluded from the analysis due to missing information (n=14), or because diagnosis was not confirmed by histopathology (n=3).

Finally, 186 patients (118 male, 68 female) with AT/RT treated between 1990 and 2016 were evaluable. In 45/186 (24%) patients, data on SMARCB1 germline mutation were available. Seven of them presented with germline pathogenic variant of SMARCB1 gene. Three patients (2%) suffered from a synchronous malignant rhabdoid tumor of the kidney. Ninety-five (51%) and 83 (45%) patients were treated according to protocols of EU-RHAB/RHABDOID 2007 and HIT-/AT/RT-ZNS studies, respectively. Eight patients (4%) received individual treatment concepts. Patients were referred from twelve European countries, the majority (n=167; 90%) from Germany.

Median age at diagnosis was 1.57 years (range, 0.01-26.70). One hundred and thirty-eight children (74%) were younger than three years at initial diagnosis. Details on patient's characteristics are presented in table 1. Metastatic disease staging according to Chang[25] was available for 173 patients (93%). M0 was in 130, M1 in 17, M2 in 6, M3 in 17 and, M4 in 3 patients, respectively. All but one patient received surgery. One hundred sixty-four patients (88%) received total or subtotal surgery. Forty-nine patients (26%) underwent a second-look resection. In 10 patients (5%), information on the extent of resection was missing. In 146 patients (78%) date of surgery (incl. date of biopsy) was considered as date of initial diagnosis for analysis. Date of surgery was missing in 40 patients (22%), therefore, date of first MRI was considered as date of initial diagnosis (with a median time of eight days between first MRI and surgery). Patients treated with RT were older compared to patients treated without. Also, M-stages differs between the groups.

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A total of 128 patients (69%) received RT in their therapy course, 104 (81%) 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 children were younger than 18 months, four of them being younger than 12 months. The interval between diagnosis and initiation of irradiation ranged from 0.03 to 1.69 years (median, 0.35 years) for patients irradiated during first line therapy. For patients treated after PD, median interval from diagnosis to RT was 0.76 years (range, 0.27-2.41 years). In patients who were younger than 18 months at diagnosis (n=40), RT was applied after median time interval of 0.64 years (range, 0.06-1.69 years). Patients older than 18 months (n=88), received RT after a median of 0.33 years (range, 0.03-2.41 years).

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 applied in 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.

Outcome of the entire cohort

The median and mean follow-up time of the entire cohort was 1.73 years and 3.31 years (range, 0.06-20.11 years), respectively. During the observation period, 122 patients (66%) experienced recurrent or progressive disease. 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% confidence interval (CI), 0.75-1.16 years) (Figure 1). The estimated 1-year and 2-year PFS rates were 48% (95% CI, 41%-55%) and 33% (95% CI, 26%-40%), respectively.

One hundred and fifteen patients (62%) died. 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) (Figure 1). The estimated 1-year and 2-year OS rates were 72% (95% CI, 65%-78%) and 49% (95% CI, 41%-56%).

Median PFS and OS of patients treated according to EU-RHAB/RHABDOID 2007 (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 (supplementary Figure 1a/b). Outcome was superior when compared to patients treated according to HIT/ATRT-ZNS studies (n=83) with 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=0.026, OS: p=0.017).

Outcome by radiotherapy within first line therapy

RT treatments were applied between 1990 and 2016. One hundred and four patients received RT within first line therapy. PD was observed in 51 patients (local n= 27, dissemination/combined (local plus dissemination) n= 24). One patient developed AML 2.53 years after RT. The patient received chemotherapy. In total, 48 patients of the RT-Group died, all caused by disease.

Patients who did not receive RT (n=58) were treated between 1993 and 2014. Forty-seven patients of this group experienced recurrent/progressive disease (local n=33, dissemination/ combined n=14). In total, 51 patients died due to disease. Figure 2a/b displays Kaplan-Meier curves of PFS and OS by radiotherapy.

Prognostic factors

On univariable Cox analysis of the entire cohort, RT, extent of surgery, age ≥ 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 age ≥ 18 months remained independent significant prognostic factors for PFS and OS (table 3).

We excluded patients with RT after PD (n=24) for a second Cox model. Results are displayed in table 4.

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Subgroup analyses

First subgroup analyses included all patients receiving RT (n=128). Median OS of patients irradiated during first line therapy (n=104) was 6.04 years (range, 0.61-20.1 years) and of patients irradiated after PD (n=24) 2.53 years (range, 0.8-11.6 years), respectively (Figure 3). Univariable analysis revealed borderline significance of improved OS for patients irradiated during first line therapy compared to patients who were irradiated after PD (p=.054).

Fourteen children were younger than 18 months (median 12 months) when RT was applied (n=11 treated during first line strategy; n=3 treated at PD after systemic therapy). All of the three children irradiated at PD died due to disease 2, 6, or 9 months after RT, respectively. Out of the eleven patients receiving RT within first line therapy, eight children experienced progressive disease after a median of 0.6 years (range, 0.09-4.76 years) and, eventually, seven died due to disease after a median of 1.1 years (range, 0.13 -5-35 years).

Further subgroup analyses evaluated dose thresholds below and above the current standard of 54 Gy. We excluded patients receiving < 40 Gy (n=3). Survival plot of patients with RT within first line therapy is displayed in supplementary Figure 2 a/b. We further evaluated the subgroup receiving ≥ 54 Gy (supplementary Figure 3 a/b). Both analyses on dose thresholds showed no differences between respective dose groups.

Last subgroup analysis evaluated M-stage and RT volume (focal RT and CSI, respectively) in patients receiving RT within first line therapy. In M0 situation (n=78), 67 patients received focal RT. Eleven patients received CSI. Progressive disease was observed in 29 patients (43%) after focal RT treatment and in seven (64%) after CSI, respectively. Twenty seven patients (40%) died after focal RT treatment and seven (64%) after CSI. Survival plots are displayed in Supplementary Figure 4a/b showing no differences between groups. In M+ (n=16), focal RT and CSI was given in 5 and 11 patients, respectively (Supplementary Figure 5a/b). After focal RT, two patients suffered from progressive disease and subsequently died. Following CSI, PD occurred in six patients. All of them died eventually.

Discussion

This retrospective analysis of a European cohort confirms RT as a significant prognostic factor for outcome in AT/RT. However, our results illustrate the overall unsatisfactory prognosis of this aggressive malignancy despite intensive treatment.

Cohort

Pooling 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). Absolute cohort size is comparable with previous SEER publications analyzing data of 174-190 children with AT/RT[1,2,13]. One of the largest series (n=361) yet contained RT treatment in only 40% of the patients[4]. In the recent NCDB analysis (n=354) with children under three years, 33% of patients received RT[26]. Other previous analyses had a significantly lower number of patients reporting institutional experiences, prospective trials, or observational studies [7,9,18,27-32].

Overall outcome

Median OS of our cohort was poor with 1.95 years (23.4 months). An analysis of the U.S. Surveillance, Epidemiology, and End Results database (SEER) with data treatments between 2000-2015 showed similar disappointing median OS times with 20-24 months[2]. Previous data of the National Cancer Database (NCDB) with treatments between 2004-2012 showed even worse median OS of 14.3 months[4]. However, our data showed better outcome with modern concepts (EURHAB/RHABDOID 2007) vs. historical schemes (HIT/ATRT-ZNS studies) and suggests that overall treatment has improved over time.

RT as prognostic factor

In the present analysis RT, extent of resection, and age ≥ 18 months were independent prognostic factors for PFS and OS in multivariable model. Our findings are in accordance with results of previous populations-based studies, registry's evaluations, as well as pooled

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data analysis showing positive impact for OS with age >1-3 years[2,4,6,9-11], and gross total resection[7-9,12]. RT has already been described as a prognostic factor, however, mostly within smaller cohorts compared to ours, inhomogeneous treatment regimes, or different handling of survivorship[1,2,8,9]. A current EU-RHAB evaluation focusing on age and DNA methylation subgroups demonstrated a negative effect on omission of RT only on univariate analysis, but not on multivariable[6]. Ninety-three patients older than one year were analyzed for impact of RT[6]. In contrast, our report contains data of 186 patients of all age groups.

Role of RT in infants & toddlers

RT is usually avoided in very young children. A SEER analysis of 190 patients with AT/RT focusing on impact of contemporary trimodality treatment, showed superior survival with a therapy including RT compared to the use of surgery and chemotherapy alone[2]. Remarkably, infants and toddlers benefited the most from RT[2]. Also other publications demonstrated the role of RT at a very young age[17,26,33]. In accordance with these studies, our results confirm 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 was not available for this cohort. Further research is necessary to investigate sequelae of this vulnerable group. In this regard, proton beam therapy (PBT) is increasingly used as a promising, sparing technique possibly avoiding side-effects[28,29,35,36]. In this analysis, however, only 19% of the irradiated patients received PBT. This is due to the fact that the analyzed treatment period started in 1990, whereas PBT was rarely offered in Europe. The availability of PBT strongly increased in the last decades[37,38], now allowing access to protons for many children with AT/RT. Jazmati et al. showed that proton beam therapy in children younger than two years of age was feasible with acceptable early late toxicity[36]. In localized ependymoma, immediate postoperative focal RT upon age of 12 months is already considered as standard[39]. The current

SIOP Ependymoma II trial (NCT02265770) established a minimum age of 12 months for RT[40]. The same cut-off is used in the current European multinational umbrella trial for patients with AT/RT (SIOPE ATRT 01, EudraCT 2018-003335-29). This European study will hopefully provide more data concerning RT in AT/RT patients in the near future.

RT within first line therapy vs. salvage RT

In young children, RT is typically postponed in order 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 with RT being part of first line strategy, especially in young (≤ three years of age) children[1]. The prospective CCG-9921 study analyzed only patients under the age of three (suffering from malignant brain tumours (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 point in the same direction. By analysing the outcome of patients irradiated during first line therapy compared to patients irradiated after PD, initially treated patients showed borderline significantly improved OS. In addition, results of our second Cox model (with patients only irradiated during first line therapy) revealed the significant impact of RT on OS. This may suggest that ‘preventive‘ RT may be preferred over salvage RT at least at higher age.

Timing of RT

Timing of RT as part of the initial therapy course is still under study. The prospective ACNS0333 study including 65 patients with AT/RT showed that timing of RT (early vs. post-consolidation) did not affect survival adversely, even though the post-consolidation administration was used for very young patients (at least 6-12 months of age) or for those with metastatic disease, both considered to be high-risk attribute[18]. We did not study detailed sequencing within initial therapy course. However, we analyzed above-mentioned timing of

RT (preventive vs. RT after PD). Cut-off for RT with regard to age was similar in all strategies in our cohort, however, individual decisions were made. In accordance with our data, results of the ACNS0333 study showed, that RT was feasible in children < 6-12 months of age[18]. Still, outcome in our cohort of 14 children under an age < 1.5 years receiving RT was poor reflecting the high-risk profile of these very young patients justifying RT. However, due to the small cohort size it was not possible to draw any conclusions for this subgroup.

Recurrence patterns

Since RT is a local treatment, recurrence patterns (local vs. disseminated) are of particular importance. Our results displayed local (and combined) failures after RT in 50% of the patients treated within first line therapy. Earlier reports showed higher rate of local (and combined) failures[6,18,42]. Nevertheless, RT is an important part of local therapy impacting on OS.

Subgroup analyses

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

Subgroup analyses on dose thresholds could not indicate any impact of dose levels below or above the current standard of 54 Gy. However, due to small numbers, results have to be interpreted with caution. The data may still support the ACNS0333 proposing a lower dose of 50.4 Gy to the primary site in very young AT/RT patients < 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 this strategy also due to small numbers. However, it may be promising that we achieved similar survival rates for patients receiving 59.4 Gy when compared to patients receiving 54 Gy, bearing in mind that residual disease was proven to have negative impact on survival.

Limitations

This analysis contains several limitations. Selection bias may have had a significant impact on the benefits of RT. The treatment regimens were inhomogeneous regarding chemotherapy, RT doses, and fractionation schemes. Additionally, different photon and proton techniques were applied, and treatment planning techniques changed over time. Today, it becomes evident that apart from modern techniques, quality assurance of RT is of high importance. Inadequate application of RT can have a significantly negative impact on outcome[44]. A recent report revealed a high rate of protocol deviations with regard to RT planning in children with medulloblastoma[45]. Pre-treatment RT quality assurance programs were strongly recommended in future clinical trials. So far, RT quality control was missing in previous AT/RT trials.

Unfortunately, some information on relevant parameters was missing. Data on late toxicity and second primary cancer was not available or incomplete. Future analyses have to evaluate these crucial aspects. It would also be interesting to assess particular parameters of modern RT techniques, and of chemotherapy (e.g. high-dose, intrathecal, substances) in order 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 this analysis. Future research has to validate the impact of these subgroups on RT.

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Conclusion

RT plays an important role in the treatment of AT/RT. However, long-term radiation-induced toxicity has to be considered to better define the role of RT in very young children. Outcomes after contemporary RT techniques have to be analyzed within prospective studies. RT quality reviews need to be an integral part of any clinical study. Future protocols will reveal efficacy of innovative treatment strategies.

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Figures captions

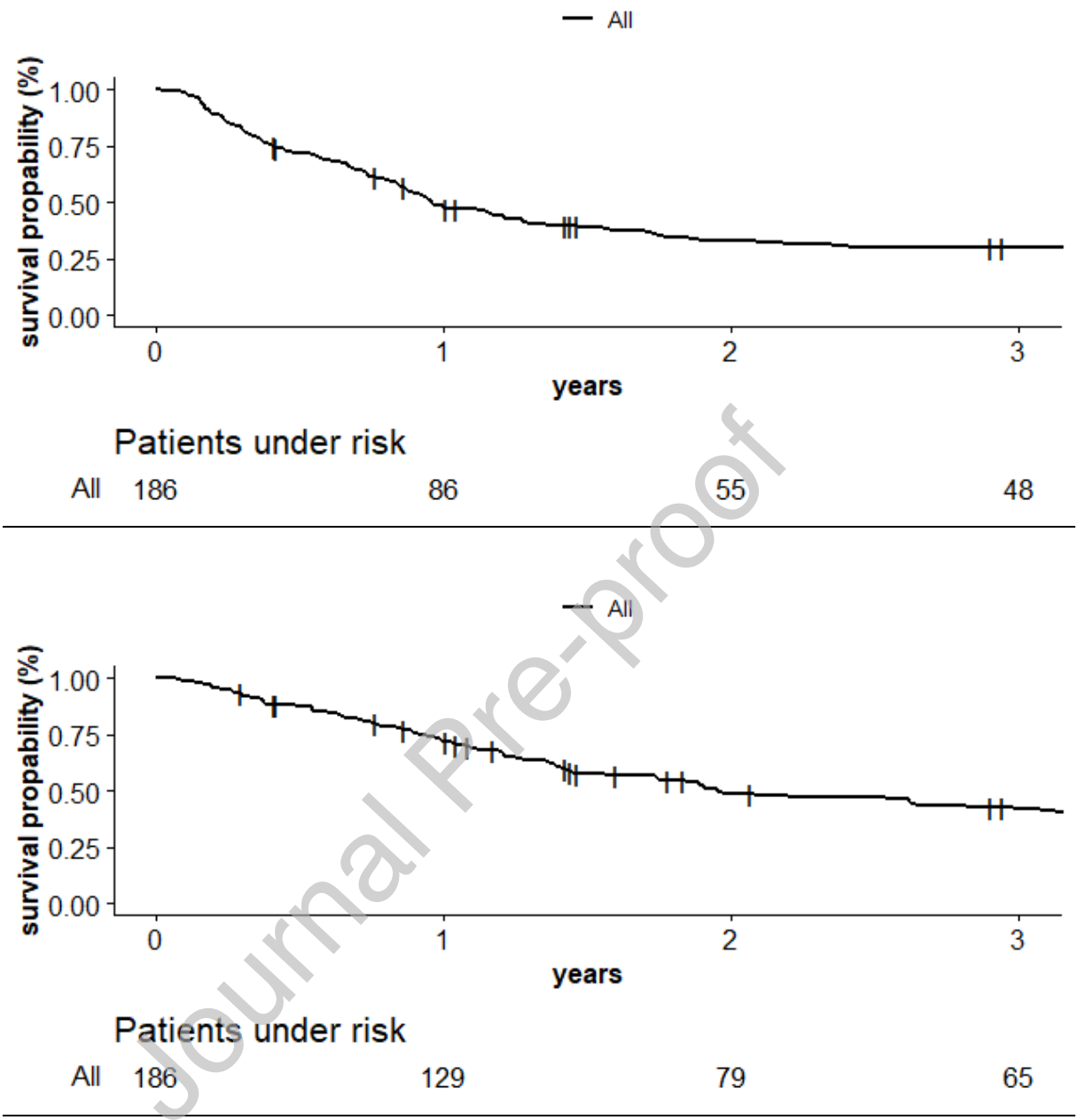

Figure 1. Kaplan-Meier plots of outcome of the entire cohort. a) Progression-free survival. The estimated 1-year and 2-year PFS rates were 48% (95% CI, 41%-55%) and 33% (95% CI, 26%-40%), respectively. b) Overall survival. The estimated 1-year and 2-year OS rates were 72% (95% CI, 65%-78%) and 49% (95% CI, 41%-56%).

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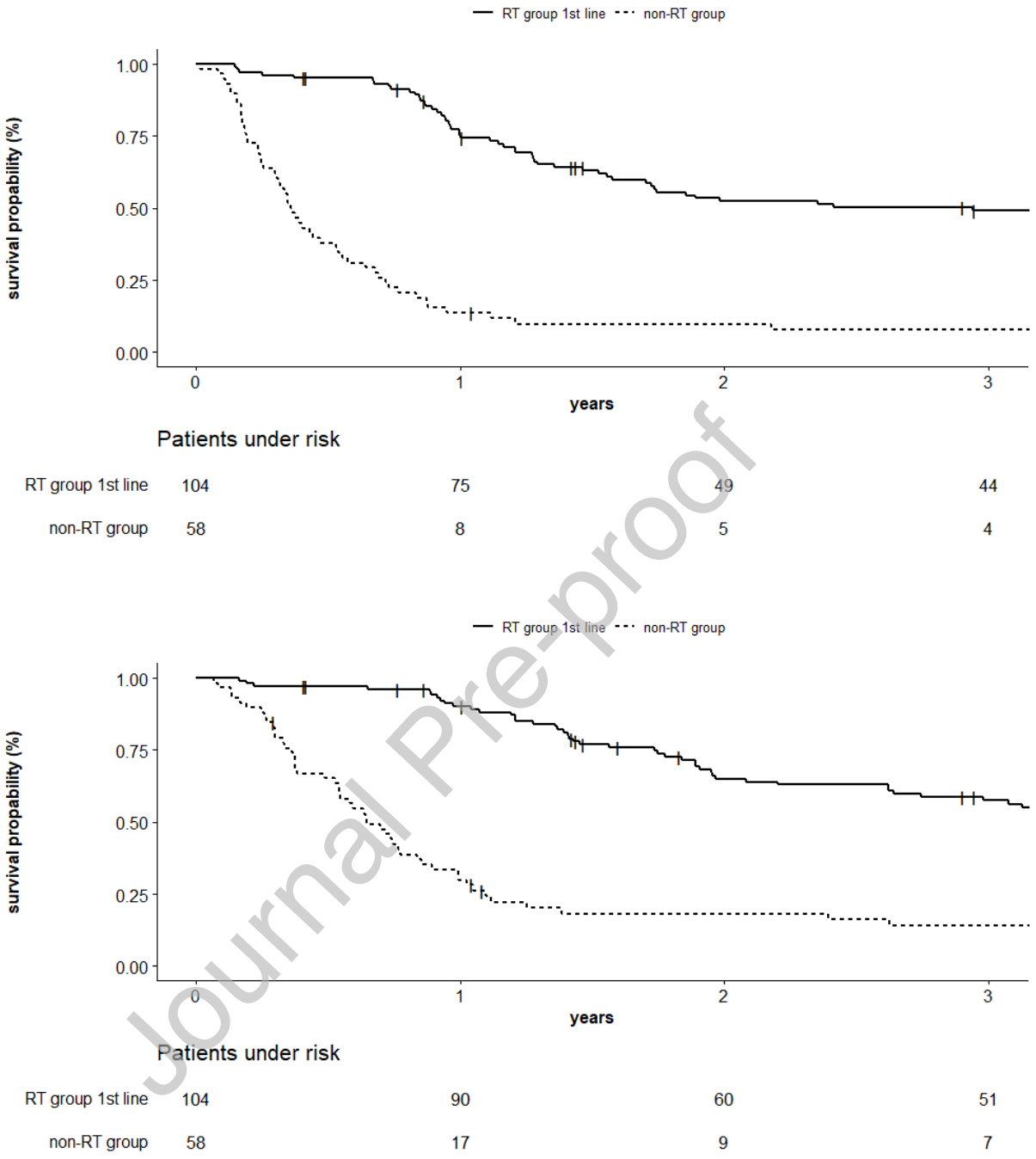

Figure 2. Kaplan-Meier plot of outcome in patients within first line therapy by radiotherapy. a) Progression-free survival. RT group: the estimated 1-year and 2-year PFS rate was 75% (95% CI, 67%-84%) and 52% (95% CI, 43%-63%), respectively. Non-RT group: the estimated 1-year and 2-year PFS rate was 14% (95% CI, 7%-26%) and 10% (95% CI, 4%-22%), respectively. b) Overall survival. RT group: the estimated 1-year and 2-year OS rate

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was 90% (95% CI, 84%-96%), and 65% (95% CI, 56%-75%), respectively. Non-RT group: The estimated 1-year and 2-year OS rate after one and two years was 30% (95% CI, 20%-45%) and 18% (95% CI, 10%-32%).

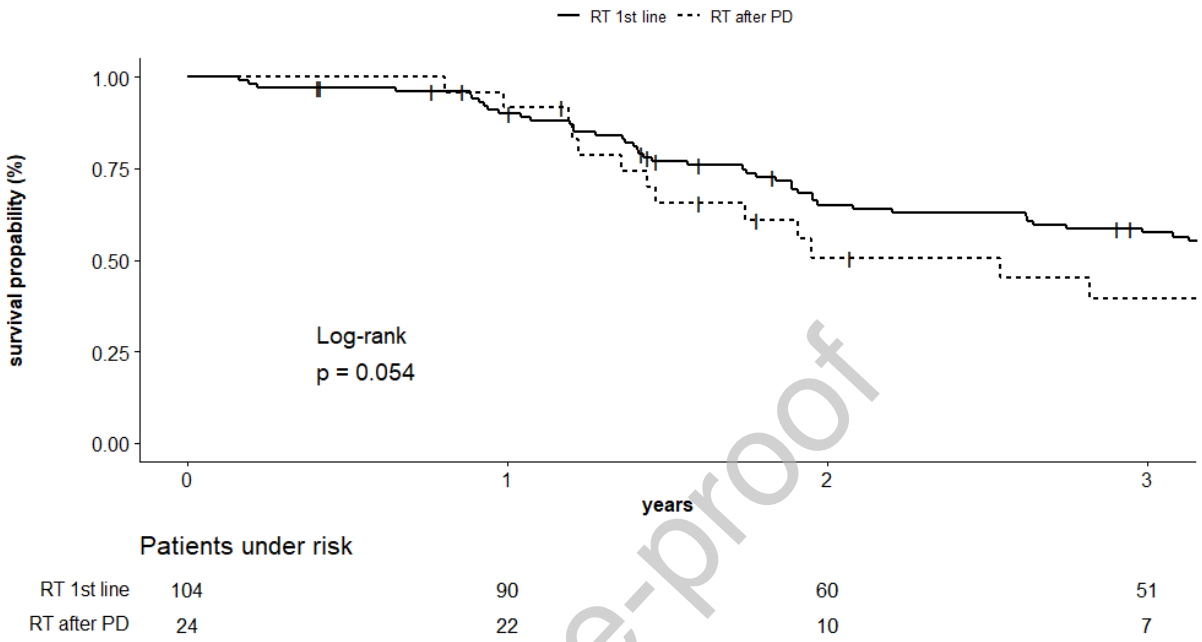

Figure 3. Subgroup analysis. Kaplan-Meier plot of overall survival in patients with radiotherapy in their therapy course by timepoint of radiotherapy (within first line therapy vs. after progressive disease).

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Table 1. Demographics, clinical and treatment characteristics in paediatric patients with atypical teratoid/rhabdoid tumours

Characteristic		**Total (n=186)**		**RT group (n=128)**		RT group, 1st line (n=104)		RT group, after PD (n=24)		**non-RT group (n=58)**		**p****
		No. of patients	(Percent)	No. of patients	(Percent)	No. of patients	(Percent)	No. of patients	(Percent)	No. of patients	(Percent)	
Gender	male	118	(63.4)	84	(65.6)	65	(62.5)	19	(79.2)	34	(58.6)	0.358
	female	68	(36.6)	44	(34.4)	39	(37.5)	5	(20.8)	24	(41.4)	
Age at diagnosis	< 18 months	87	(46.8)	40	(31.3)	28	(26.9)	12	(50.0)	47	(81.0)	<0.001
	≥ 18 months	99	(53.2)	88	(68.8)	76	(73.1)	12	(50.0)	11	(19.0)	
Location	supratentorial	80	(43.0)	48	(37.5)	37	(35.6)	11	(45.8)	32	(55.2)	0.078
	infratentorial	13	(7.0)	10	(7.8)	10	(9.6)	1	(4.2)	3	(5.2)	
	bifocal	5	(2.7)	2	(1.6)	2	(1.9)	1	(4.2)	3	(5.2)	
	spinal	1	(0.5)	1	(0.8)	1	(1.0)	0	(0.0)	0	(0.0)	
	n.s.	87	(46.8)	67	(52.3)	54	(51.9)	13	(54.2)	20*	(34.5)	
Metastases at diagnosis	M0	130	(69.9)	96	(75.0)	79	(76.0)	17	(70.8)	34	(58.6)	0.006
	M1-M4	43	(23.1)	22	(17.2)	16	(15.4)	6	(25.0)	21	(36.2)	
	n.s.	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)	0.957
	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)	0	(0.0)	6	(10.3)	
	extent of res. n.s	10	(5.9)	6	(4.7)	6	(5.8)	0	(0.0)	4	(6.9)	
	no resection	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	
Chemotherapy	received	178	(95.7)	125	(97.7)	101	(97.1)	24	(100)	53	(91.4)	0.134
	none	6	(3.2)	2	(1.6)	2	(1.9)	0	(0.0)	4	(6.9)	
	n.s.	2	(1.1)	1	(0.8)	1	(1.0)	0	(0.0)	1	(1.7)	

* three patients with synchronous tumor of the kidney

** Chi-squared test RT-group vs. non-RT group

Abbreviations: No. = number; res. = resection; n.s. = not specified; PD = progression disease

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Table 2. Demographics and treatment parameters of radiotherapy

Parameters		**RT group (n=128)**	RT group, 1st line (n=104)	RT group, after PD (n=24)
		No. of patients (Percent)	No. of patients (Percent)	No. of patients (Percent)
Age at RT	< 18 months	14 (10.9)	11 (10.6)	3 (12.5)
	≥ 18 months	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)	
	photons/protons	1 (0.8)	1 (1.0)	
	n.s.	5 (3.9)	4 (3.8)	1 (4.2)
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: RT, radiotherapy; CSI, craniospinal irradiation; Gy, Gray; n.s. = not specified; PD = progression disease

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

	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
Radiotherapy								
No	Reference group		Reference group		Reference group		Reference group	
Yes	0.41 (0.27-0.63)	< .001	0.45 (0.27-0.75)	.002	0.47 (0.30-0.73)	< .001	0.54 (0.32-0.93)	.025
Resection								
biopsy only	Reference group		Reference group		Reference group		Reference group	
subtotal	0.49 (0.25-0.95)	.033	0.43 (0.22-0.85)	.015	0.38 (0.19-0.77)	.007	0.35 (0.17-0.71)	.004
gross total	0.28 (0.14-0.58)	< .001	0.29 (0.13-0.61)	.001	0.20 (0.09-0.43)	< .001	0.19 (0.08-0.42)	< .001
Age category								
≥ 18 months	Reference group		Reference group		Reference group		Reference group	
< 18 months	2.12 (1.50-2.99)	< .001	1.67 (1.12-2.47)	.011	2.21 (1.52-3.20)	< .001	1.79 (1.17-2.73)	.008
Gender								
female	Reference group		Reference group		Reference group		Reference group	
male	0.95 (0.66-1.35)	.754	1.01 (0.69-1.47)	.979	0.87 (0.60-1.27)	.474	1.00 (0.67-1.50)	.999
Metastases								
M+ (M1-M4)	Reference group		Reference group		Reference group		Reference group	
M0	0.61 (0.41-0.90)	.013	0.80 (0.52-1.23)	.306	0.57 (0.38-0.86)	.008	0.71 (0.46-1.11)	.130

Abbreviations: HR, hazard ratio; CI, confidence interval

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

	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
Radiotherapy								
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	.011 < .001	Reference group	.009 .001	Reference group	.016 < .001	Reference group	.006 < .001
subtotal	0.42 (0.22-0.82)		0.40 (0.20-0.79)		0.42 (0.21-0.85)		0.36 (0.18-0.75)	
gross total	0.23 (0.11-0.48)		0.27 (0.12-0.59)		0.19 (0.08-0.41)		0.15 (0.07-0.36)	
Age category								
≥ 18 months	Reference group	< .001	Reference group	.007	Reference group	< .001	Reference group	.099
< 18 months	2.24 (1.53-3.29)		1.88 (1.19-2.97)		2.24 (1.50-3.34)		1.50 (0.59-1.40)	
Gender								
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; CI, confidence interval

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Conflict of Interest:

JG has received honoraria from TESARO, QUIRIS Healthcare, Ecker+Ecker, Dr August Wolff, Roche, University Clinics Schleswig-Holstein, and RWTH Aachen University.

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