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RESEARCH ARTICLE

Second-line treatment of pediatric patients with relapsed rhabdomyosarcoma adapted to initial risk stratification: Data of the European Soft Tissue Sarcoma Registry (SoTiSaR)

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Abbreviations: ACCTTIVE, adriamycin, carboplatin, cyclophosphamide, topotecan, vincristine, etoposide + oral trofosfamide, idarubicin, etoposide; ARMS, alveolar rhabdomyosarcoma; CHT, chemotherapy; CI, confidence interval; CR, complete remission; CWS, Cooperative Weichteilsarkom Studiengruppe; DCEI, doxorubicin, carboplatin, etoposide, ifosfamide; EFS, event-free survival; EpSSG, European Pediatric Soft Tissue Sarcoma Study Group; ERMS, embryonal rhabdomyosarcoma; HR, high-risk group; IRS, International Rhabdomyosarcoma Study Group; LR, low-risk group; OS, overall survival; O-TIE, oral trofosfamide, idarubicin, etoposide; PD, progressive disease; PR, partial response; RMS, rhabdomyosarcoma; RT, radiotherapy; sCHT, second-line chemotherapy; SD, stable disease; SoTiSaR, Soft Tissue Sarcoma Registry; SR, standard-risk group; TECC, topotecan, etoposide, carboplatin, cyclophosphamide; TTR, time to relapse; VAIA, vincristine, actinomycin-D, ifosfamide, doxorubicin; VHR, very high-risk group.

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Abstract

Background: Outcome of relapsed disease of localized rhabdomyosarcoma remains poor. An individual treatment approach considering the initial systemic treatment and risk group was included in the Cooperative Weichteilsarkom Studiengruppe (CWS) Guidance.

Methods: Second-line chemotherapy (sCHT) ACCTTIVE based on anthracyclines (adriamycin, carboplatin, cyclophosphamide, topotecan, vincristine, etoposide) was recommended for patients with initial low- (LR), standard- (SR), and high-risk (HR) group after initial treatment without anthracyclines. TECC (topotecan, etoposide, carboplatin, cyclophosphamide) was recommended after initial anthracycline-based regimen in the very high-risk (VHR) group. Data of patients with relapse (n = 68) registered in the European Soft Tissue Sarcoma Registry SoTiSaR (2009–2018) were retrospectively analyzed.

Results: Patients of initial LR (n = 2), SR (n = 16), HR (n = 41), and VHR (n = 9) group relapsed. sCHT consisted of ACCTTIVE (n = 36), TECC (n = 12), or other (n = 15). Resection was performed in 40/68 (59%) patients and/or radiotherapy in 47/68 (69%). Initial risk stratification, pattern/time to relapse, and achievement of second complete remission were significant prognostic factors. Microscopically incomplete resection with additional radiotherapy was not inferior to microscopically complete resection (p = .17). The 5-year event-free survival (EFS) and overall survival (OS) were 26% (±12%) and 31% (±14%). The 5-year OS of patients with relapse of SR, HR, and VHR groups was 80% (±21%), 20% (±16%), and 13% (±23%, p = .008), respectively.

Conclusion: Adapted systemic treatment of relapsed disease considering the initial risk group and initial treatment is reasonable. New treatment options are needed for patients of initial HR and VHR groups.

KEYWORDS
localized disease, relapsed disease, rhabdomyosarcoma, second-line chemotherapy, Soft Tissue Sarcoma Registry (SoTiSaR)

1 | INTRODUCTION

Pediatric patients with relapsed disease of rhabdomyosarcoma (RMS) are reported to respond poorly to treatment, leading to a dismal 5-year overall survival (OS) of about 20%.[1–3] Main prognostic factors at relapse were identified as the type of recurrence, time to relapse (TTR), initial tumor size, and prior irradiation.[2] For relapse treatment in patients with first relapse of RMS, two clinical trials have been conducted by the Children's Oncology Group[1,4]: ARST0121 evaluated a risk-based approach stratifying patients into favorable risk treated with the doxorubicin, cyclophosphamide, etoposide, ifosfamide schedule (DCEI), resulting in a 3-year failure-free survival rate of 79%, and unfavorable risk treated with DCEI plus vincristine and irinotecan (VI), with a reported 3-year OS of 20%. The randomized phase II study ARST0921 evaluated the combination of cyclophosphamide and vinorelbine with temsirolimus or bevacizumab, revealing a superior 6-month event-free survival (EFS) for temsirolismus (69% vs. 55%).[5] Therefore, temsirolimus is currently undergoing evaluation for front-line therapy in a randomized clinical trial (NCT02567435).

The European Soft Tissue Sarcoma Study Group (EpSSG) performed the phase-II trial for relapsed or refractory RMS, evaluating the second-line chemotherapy (sCHT) vincristine plus irinotecan with or without temozolomide (VI vs. VIT). Regarding the whole cohort, 2-year EFS and OS were superior in the VIT arm (19% and 33%), whereas EFS and OS were similar when patients with refractory disease are excluded.[3] In the ongoing FaR-RMS trial (NCT04625907), the combination of VI with a multikinase inhibitor (regorafenib) will be tested. Despite these ongoing efforts, survival of pediatric patients with relapsed RMS remains poor and improvement in treating these patients is needed.

The Cooperative Weichteilsarkom Studiengruppe (CWS) established CWS Guidance, summarizing treatment recommendations for patients registered in the European Soft tissue Sarcoma registry (SoTiSaR) similar to the standard regimens in RMS 2005.[6–9] Based on study data on patients with RMS and Ewing sarcoma showing the effectiveness of carboplatin with etoposide in embryonal rhabdomyosarcoma (ERMS) by inducing a second remission in 40% of patients,[10] treatment recommendations for relapsed RMS were included into CWS

Guidance. These treatment recommendations followed an individualized approach, taking into account the risk stratification and treatment applied in primary disease, and comprised systemic multimodal treatment, including second-line CHT based on carboplatin and etoposide[10] in combination with anthracyclines plus alkylating agents[1] (ACCTTIVE: adriamycin, carboplatin, cyclophosphamide, topotecan, vincristine, etoposide + oral trofosfamide, idarubicin, etoposide) or in combination with topotecan[11] (TECC: topotecan, etoposide, carboplatin, cyclophosphamide).

The primary objective of this study is to describe the experience, responses, and outcomes with ACCTTIVE and TECC in the relapsed RMS setting. The secondary objective is to define prognostic risk factors of relapsed localized RMS.

Informed consent has been obtained from all participating patients and/or their parents/guardians according to the legal requirements.

2 | METHODS

2.1 | Patients

Inclusion criteria were an age of 0–21 years, diagnosis of first relapse of RMS, and central pathology revision. The complete dataset including patient characteristics and treatment of initial and relapsed disease was mandatory. Patients diagnosed between 2009 and 2018 with documented event of relapse after achieving complete remission (CR) until 2019 were included, with follow-up until December 2021. Patients with progressive disease (PD) under first-line treatment without achieving CR are not included in the analysis but reported descriptively.

2.2 | Definition of terms at initial disease

In primary disease, clinical staging was performed assessing tumor extension by magnetic resonance imaging or computed tomography. The tumor-node-metastasis (TNM) classification was used as previously described.[12] Resection margins were defined at the time of pathological assessment and led to postsurgical staging adapted from the International Rhabdomyosarcoma Study Group (IRS).[13] Resection status was classified as microscopically complete (R0/IRS group I), macroscopically complete (R1/IRS group II), or macroscopically incomplete after primary resection or after biopsy as primary surgical procedure (R2/IRS group III). Patients were stratified according to the common CWS/EpSSG RMS stratification used in CWS Guidance and RMS 2005[7] to low (LR), standard (SR), high (HR), and very high-risk (VHR) groups based on N-status, histology, IRS group, tumor site, and size/patient's age[16] (Table S1). Favorable tumor site was defined as orbital, head/neck non-parameningeal, urogenital non-bladder/prostate. All other tumor sites were classified as unfavorable according to CWS Guidance/RMS 2005. Tumor volume at diagnosis and after three CHT cycles (7—10 weeks), in patients with measurable disease (IRS group III), was estimated by three-dimension method and used for tumor response evaluation defined as: CR (complete disappearance of the tumor), very good partial response (PR >90%), PR (PR ≥2/3, former "good response"[18]), minor PR (PR <2/3, former "poor response," and "objective response"[18]), PD or stable disease (SD, Table S2). For the purpose of this analysis, all PR were summarized to one group. Best surgery was defined as the best surgical result of multiple resections. Patients with refractory/PD never reached CR.

2.3 | Definition of terms at relapsed disease

Relapsed disease was defined as any new tumor appearance after CR. The interval between achievement of first CR and detection of relapse was defined as TTR.[14] A radiological staging was performed after histologic confirmation of relapse to differentiate between locoregional, metastatic, or combined relapse. Response to second-line CHT was assessed through radiologic assessment after two to four courses of CHT and classified as CR, PR, SD, or PD analogous to primary disease. Best surgery was defined according to the definitions in primary disease.

2.4 | Treatment of primary disease

All patients received multimodal treatment of localized RMS including CHT and local treatment. CHT comprised vincristine and actinomycin-D (VA) in the LR group, combined with an alkylating agent in SR and HR group. Anthracyclines were recommended (vincristine, dactinomycin, ifosfamide, doxorubicin, VAIA) in the VHR group.[15] Maintenance CHT was not regularly indicated as patients were assigned to the CWS-2007 HR trial, which included the randomization of stop of treatment or continuation with oral treatment with idarubicin, trofosfamide, and etoposide (O-TIE) for 6 months[16] based on results of the HD CWS-96 and CWS-2002P studies.[16,18] Delayed resection was applied in all patients with IRS stage II/III. Radiotherapy (RT) was indicated according to the CWS guidance analogous to RMS 2005[8,9,19] (Table S3).

2.5 | Treatment of relapsed disease

Second-line CHT ACCTTIVE (adriamycin, carboplatin, cyclophosphamide, topotecan, vincristine, ± oral maintenance with trofosfamide, ifosfamide, etoposide) based on anthracyclines (300 mg/m^2) was recommended in LR, SR, and HR patients after primary therapy with IVA (ifosfamide, vincristine, dactinomycin). In patients with HR or VHR regimen, TECC (topotecan, etoposide, carboplatin, cyclophosphamide, Figure S1) was recommended after primary therapy with VAIA. Maintenance therapy with O-TIE or cyclophosphamide/vinblastine was offered for patients who achieved complete or very good partial remission.[16,18] Local control with delayed resection and/or RT was aimed to achieve a second CR, preferably after response to second-line CHT analogous to the time point of the primary treatment. Mutilating surgery was performed as individual decision of the treating center. RT doses were adapted to initial RT according to individual decisions of the treating centers.

2.6 | Treatment of refractory/progressive disease

No treatment recommendations on refractory or PD are included in the CWS Guidance. Patients were treated on individual decision of the treating centers.

2.7 | Data collection and evaluation

Guardians of patients enrolled in SoTiSaR had previously consented to data collection. Retrospective chart review was performed per the requirements of the Declaration of Helsinki and in accordance with the respective ethical committee.

Pathological reviews were performed at the Institute for Pathology in Kiel and Bonn, Germany. The PAX/FOXO1 fusion gene status was analyzed by fluorescence in situ hybridization and/or real-time polymerase chain reaction.[20–22] In addition to the data available in the database obtained by yearly status reports, medical reports were studied by the first author.

2.8 | Statistical methods

Statistical analyses were conducted using IBM SPSS 26 (Armonk, NY, USA). OS and EFS were calculated using the Kaplan–Meier estimator,[23] and with confidence intervals (CI) stated at the 95% level. OS was calculated as the time from detection of relapse to death or last follow-up. EFS was calculated as the time from detection of relapse to progression, second relapse after CR, or last follow-up. If there was no event, survival data were censored at last follow-up. For comparison of EFS or OS levels across potential risk groups, the log-rank test was used. EFS and OS at 5 years were calculated, except when all patients were censored before reaching 5 years. For comparison with international protocols, EFS was also calculated on 2-year and 3-year levels. All statistical tests were conducted at $\alpha = .05$. Following conventions, statistically significant results are marked with an asterisk (*) when they reach $p < .05$ and with (**) when they reach $p < .001$. The research reported is exploratory and given that the sample size is relatively small *p*-values are not adjusted for multiple testing. Descriptive statistics are depicted as median [range], if not otherwise specified.

3 | RESULTS

3.1 | Patient characteristics and demography

Overall, 835 patients with RMS were registered in SoTiSaR. Primary disease was localized in 591/835 (71%) patients, and 149/591 (25%) showed an event. From 149 events, 93 were classified as relapse, from which 25 were excluded from the analysis as they did not fulfill inclusion criteria (follow-up time, age, insufficient data, no CHT, no reference proven histology, no true relapse; Figure 1). In total, 68 patients with relapsed RMS were eligible for this analysis including patients from Germany ($n = 56$), Switzerland ($n = 10$), and Sweden ($n = 2$). Median age at relapse was 6.9 years [1–21], with a median TTR of 1.2 years [0.3–4.6], based on a median follow-up of 3.2 years [0.9–8.3] from primary diagnosis. Median follow-up after relapse was 1.7 years [0.08–6.8]. Fusion status was available for all alveolar rhabdomyosarcoma (ARMS) patients: PAX3/FOXO1 ($n = 21$), PAX7/FOXO1 ($n = 4$), PAX3/NCOA ($n = 2$), FOXO break ($n = 2$). All examined ERMS patients were fusion-negative ($n = 8/34$).

Fifty-six patients with RMS had refractory/PD on initial treatment and 48 patients with complete dataset were included descriptively (Figure 1).

3.2 | Treatment of primary disease

All 68 patients received multimodal treatment for their primary disease (Table 1). Patients were treated according to LR ($n = 2$), SR ($n = 16$), HR ($n = 41$), and VHR groups ($n = 9$). In the IRS III group ($n = 55$), 47 patients underwent biopsy and eight primary R2 resection. Location in head and neck was the most frequent tumor localization ($n = 28$). Primary CHT consisted of VA in the two LR patients and IVA in all SR and all but two HR patients ($n = 55$) who were treated with VAIA based on decision of treating center. All 11 patients in VHR group received VAIA CHT. Oral maintenance treatment (O-TIE) was administered to patients of the HR group ($n = 4$) and SR ($n = 1$) as individual decision. Response was assessable in 44 patients and revealed CR ($n = 4$) and PR ($n = 40$). A delayed secondary resection was performed in 25 IRS III patients, resulting in R0 ($n = 16$) or R1 status ($n = 9$). In 30 patients (54%), no resection was possible resulting in R2. Radiation of the tumor was performed in 41 patients (59%), with a median dose of 50.4 Gy [36–68.4]. Patients were irradiated after surgery ($n = 11$), before surgery ($n = 2$), or received RT only ($n = 24$), no data available ($n = 4$).

3.3 | Treatment of relapsed disease

Relapsed disease was localized in 71% ($n = 48$), metastatic in 21% ($n = 14$), and combined in 9% ($n = 6$) of patients (Table 2). An early relapse (within 6 months) occurred in 21% ($n = 14$), an intermediate relapse (6–12 months) in 41% ($n = 28$), and a late relapse (>12 months) in 38% ($n = 26$) of patients [2–52 months]. Second-line treatment was administered to 94% ($n = 63$) of patients: ACCTTIVE ($n = 36$), TECC ($n = 12$), and other ($n = 15$). Five patients did not receive CHT as individual decision of the patient/parents and died within 65 days (median, range 28–86). Second-line CHT was applied for an average 25 weeks (eight cycles). Assessable response evaluation after a median of three cycles [range: 1–5 cycles] showed CR ($n = 4$) and PR ($n = 31$). No response was seen in 13 patients: PD ($n = 8$) and SD ($n = 5$).

A complete dataset on second-line CHT was available in 59/68 patients, five patients did not receive any systemic treatment, and in four patients, it was unclear if second-line treatment was completed as scheduled. In 11 of the evaluable 59 patients, second-line CHT

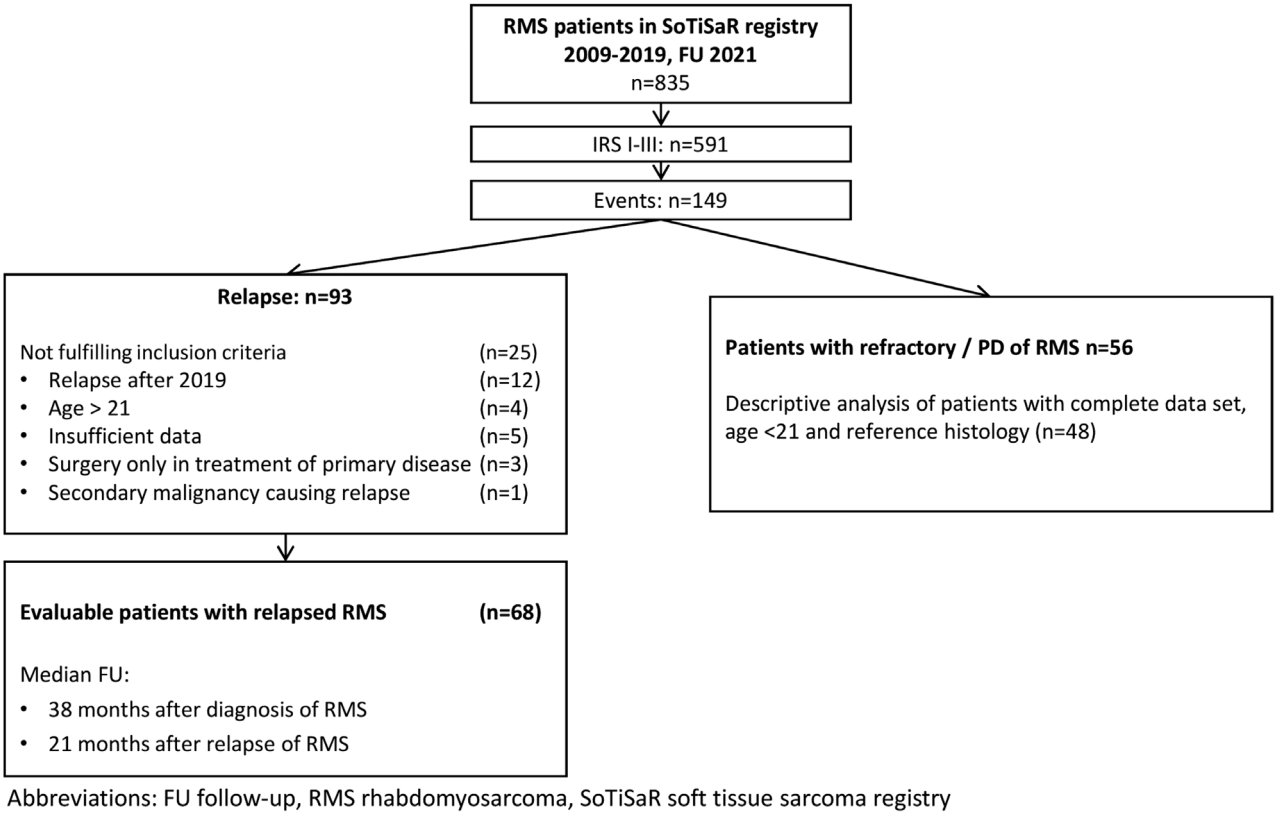

FIGURE 1 Selection of patients eligible for this study (consort diagram).

was discontinued because of SD or PD at response imaging. Five of these 11 patients received third-line CHT. After end of intensive treatment, 28/68 patients were treated with maintenance therapy (9/16 SR, 15/41 HR, 4/9 VHR patients) with O-TIE ($n = 25$) or cyclophosphamide/vinblastine ($n = 3$) with a median duration of 34 weeks [6–44] as individual treatment decision.

Primary resection of relapsed disease was feasible in 15 patients (22%), resulting in R0 ($n = 6$), R1 ($n = 6$), and R2 resections ($n = 2$), missing data in one patient. After second-line CHT, a delayed resection was performed in 25 patients, resulting in R0 ($n = 13$), R1 ($n = 7$), and R2 resections ($n = 5$). RT as the only local treatment was performed in 16 patients. Two out of 16 patients received RT with palliative intention only and were excluded for analysis of RT as treatment approach. RT was given to 31 patients after surgery (11/19 after R0, 12/12 after R1, six of seven after R2 resection, no data on two patients). RT modality was proton-based ($n = 14$), photon ($n = 13$) and brachytherapy ($n = 4$: two orbital, two urogenital tumors), 16 patients were irradiated with unknown modality. Mean applied dose was 43 Gy [28–56] (available data of $n = 15$).

3.4 | Patients with progressive disease

Forty-eight patients were reported to have PD: ERMS ($n = 32$). ARMS ($n = 13$), spindle-cell RMS ($n = 2$), and pleomorphic RMS ($n = 1$). The initial risk group was SR ($n = 7$), HR ($n = 31$), and VHR ($n = 7$), no data available ($n = 3$). Disease was progressive during primary treatment ($n = 3$) and within few weeks after the end of intensive treatment without reaching CR ($n = 42$). Mean follow-up after progression was 1.8 years. Fourteen patients (29%) were alive at end of follow-up, whereas the other 34 patients (71%) succumbed to their disease after a mean duration of 0.64 years. These patients are not included in the calculations of the analysis as they did not fulfill the criteria.

3.5 | Toxicity and long-term effects

Acute hematotoxicity grade 3–4 was reported in 17 out of 49 patients with available data. Stop of second-line treatment due to acute chemo-related toxicity was reported in four patients (ca. 7%, 95% $CI_{Clopper-Pearson}$: 2%–16%) with consecutive switch to third-line ($n = 3$) or end of second-line CHT ($n = 1$): nephropathy ($n = 2$), severe hematotoxicity ($n = 1$), unknown ($n = 1$). Long-term toxicity was reported in 11 patients, details were available in four of 11: chronic kidney injury ($n = 3$) and permanent hearing loss ($n = 1$).

3.6 | Overall outcome and prognostic factors

The 5-year EFS and OS after diagnosis of relapse of the whole cohort were 26% (±12%, 95% CI) and 31% (±14%, 95% CI), respectively (Figure 2). Initial risk stratification was a significant prognostic factor

TABLE 1 Univariable analysis of 68 patients with primary localized disease.

	n	%	5-year EFS ± 95% CI (%)	*p* (EFS)		5-year OS ± 95% CI (%)	*p* (OS)
Gender							
Female	31	46	28 ± 20	.22		36 ± 21	.12
Male	37	54	25 ± 16			28 ± 20	
Age							
≤1 year	6	9	–	.11		00 ± 00	.60
>1 year ≤10 years	42	61	31 ± 18			35 ± 20	
>10 years ≤21 years	20	29	18 ± 18			27 ± 23	
Histology							
ERMS	34	51	39 ± 20	.11	.21	38 ± 21	.8
ARMS	29	42	11 ± 14			22 ± 20	
RMS spindle cell	5	7	20 ± 35			–	
Primary tumor size (cm)[a]							
≤5 cm	31	46	37 ± 20	.07		35 ± 21	.16
>5 cm	34	50	15 ± 16			26 ± 20	
Primary tumor site							
Favorable	20	29	44 ± 25	.03*		53 ± 28	.03*
Unfavorable	48	71	19 ± 13			24 ± 15	
IRS group							
I	4	6	00 ± 00	.38		00 ± 00	.62
II	9	13	50 ± 37			42 ± 41	
III	55	81	23 ± 14			30 ± 16	
Tumor invasiveness[a]							
T1	24	35	26 ± 20	.39		40 ± 25	.08
T2	33	49	24 ± 18			25 ± 20	
N status[a]							
N0	50	74	28 ± 16	.11		30 ± 18	.37
N1	15	22	15 ± 20			35 ± 25	
Initial risk group							
Low risk	2	3	–	.002*		–	.008*
Standard risk	16	24	73 ± 23			80 ± 21	
High risk	41	60	12 ± 12			20 ± 16	
Very high risk	9	13	15 ± 25			13 ± 23	
Best surgery at primary disease							
R0	23	34	23 ± 20	.045*		27 ± 23	.52
R1	15	22	25 ± 39			56 ± 27	
R2	6	9	00 ± 00			00 ± 00	
Biopsy	24	35	22 ± 20			27 ± 23	
Chemotherapy at primary disease							
VA/IVA	57	84	28 ± 14	.02*		35 ± 18	.007*
VAIA	11	16	11 ± 21			10 ± 20	
Response to initial CHT[a]							
CR	4	6	00 ± 00	.45		38 ± 57	.94
PR	40	59	23 ± 14			31 ± 18	
RT at primary disease[a]							
Yes	41	60	21 ± 14	.13		37 ± 27	.25
No	23	34	34 ± 21			26 ± 16	

Note: Favorable primary tumor site: orbital, head/neck non-parameningeal, urogenital non-bladder/prostate; unfavorable: all other tumor sites.

Abbreviations: ARMS, alveolar rhabdomyosarcoma; CHT, chemotherapy; EFS, event-free survival; ERMS, embryonal rhabdomyosarcoma; (I)VA, (ifosfamide), vincristine, actinomycin-D; OS, overall survival; *p*, *p*-value using log-rank test; R0, microscopic complete resection; R1, microscopic incomplete resection; R2, macroscopic incomplete resection; RT, radiotherapy; VAIA, vincristine, actinomycin-D, ifosfamide, doxorubicin; –, all events censored before reaching 5-year follow-up.

[a]Patients with unknown data were excluded from the statistical analysis.

*Significance on $p = .05$ level; **significance on $p = .001$ level.

TABLE 2 Univariable analysis of 68 patients after relapse.

	n	%	5-year EFS ± 95% CI (%)	*p* (EFS)		5-year OS ± 95% CI (%)	*p* (OS)	
Age at relapse								
≤10 years	45	66	26 ± 17	.26		29 ± 19	.99	
>10 years	23	34	23 ± 19			34 ± 23		
Time CR to relapsed disease (TTR)								
≤6 months	14	21	18 ± 21	<.001**		12 ± 23	<.001**	
6–12 months	28	41	12 ± 12			21 ± 18		
≥12 months	26	38	49 ± 25			62 ± 29		
Type of relapse								
Local	48	70	37 ± 17	<.001**		42 ± 18	<.001**	
Metastatic	14	21	00 ± 00			00 ± 00		
Combined	6	9	00 ± 00			–		
Surgery at relapse								
Yes	40	59	31 ± 17	.003*		34 ± 19	.011*	
No	28	41	19 ± 17			30 ± 22		
Best surgery at relapse[a]								
R0	19	28	16 ± 23	.06	.001*	16 ± 25	.17	.025*
R1	12	18	71 ± 29			67 ± 31		
R2	7	10	–	.83		–	.34	
No resection	28	41	19 ± 18			30 ± 21		
Timing of relapse surgery in patients with local relapse								
Primary resection	15	31	48 ± 33	.08		50 ± 35	.14	
Delayed resection	33	69	32 ± 18			37 ± 21		
Radiotherapy at relapse[a]								
Yes	46	68	30 ± 16	.014*		39 ± 18	.045*	
No	20	30	19 ± 19			13 ± 22		
Salvage chemotherapy at relapse								
ACCTTIVE	36	53	32 ± 18	.001**	.15	40 ± 21	.001**	.062
TECC	12	18	10 ± 18			19 ± 23		
VAIA/CEVAIE	8	6	37 ± 39			35 ± 38		
Other	7	4	–			–		
None	5	7	00 ± 00			00 ± 00		
Salvage maintenance therapy at relapse								
Yes	28	41	28 ± 19	.10		28 ± 20	.34	
No	40	59	26 ± 16			32 ± 19		
Response to salvage CHT at relapse[a]								
CR	4	6	–	.31		–	.33	
PR	31	46	23 ± 16			31 ± 19		
SD	5	7	–			–		
PD	8	12	00 ± 00			00 ± 00		
Outcome after relapse therapy[a]								
CR	43	63	35 ± 18	<.001**		41 ± 19	<.001**	
Non-CR	23	34	10 ± 13			–		

Abbreviations: ACCTTIVE, adriamycin, carboplatin, cyclophosphamide, topotecan, vincristine, etoposide ± maintenance therapy (trofosfamide, ifosfamide, etoposide); CEVAIE, carboplatin, epirubicin, vincristine, actinomycin-D, ifosfamide, etoposide; CHT, chemotherapy; EFS, event-free survival; OS, overall survival; *p*, *p*-value using log-rank test; R0, microscopic complete resection; R1, microscopic incomplete resection; R2, macroscopic incomplete resection; TECC, topotecan, etoposide, carboplatin, cyclophosphamide; TTR, time to relapse; VAIA, vincristine, actinomycin-D, ifosfamide, doxorubicin; –, all events censored before reaching 5-year follow-up.

[a]Patients with unknown data were excluded from the statistical analysis.

*Significance at $p = .05$; **significance at $p = .001$.

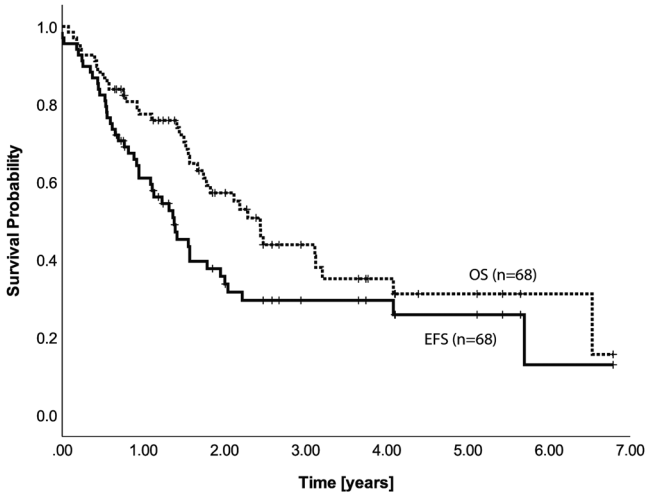

FIGURE 2 Event-free survival (EFS) and overall survival (OS) for the whole cohort investigated ($n = 68$).

(Table 1): patients with relapsed disease after initial SR group had a 5-year OS of 80% (±21%, 95% CI, $n = 16$), in contrast to patients after initial HR group with a 5-year OS of 20% (±16%, 95% CI, $n = 41$) and after initial VHR group with 13% (±23%, 95% CI, $n = 9$). Patients of initial LR group were included in the calculations but no 5-year EFS/OS could be assessed due to loss of follow-up. Unfavorable primary tumor site was associated with poor OS and EFS. Patients receiving R0, R1 resection or biopsy at initial diagnosis had better EFS compared to R2 resected patients ($p = .045$), but not OS ($p = .52$). Significant prognostic factors in the relapsed setting were TTR, type of relapse, the second-line CHT regimen, achievement of second CR (Table 2, Figure 3A–D). No significant difference between surgery alone, radiation alone, or a combination of RT and surgery was found (Figure 4). Best surgery at relapsed disease significantly improved prognosis ($p < .001$ for EFS, 0.025 for OS). There is insufficient evidence based on these data to support a difference between R0 resection alone and R1 resection with adjacent RT: 5-year OS 16% (±25%, 95% CI) for R0, 67% (±31%, 95% CI) for R1 ($p = .17$) or R0 resection plus adjacent RT (5-year OS: 0% for R0+RT, 67% (±16%, 95% CI) for R1+RT ($p = .12$).

Most patients with localized relapse underwent primary resection. Looking at the time point of resection, patients with primary resection of the localized relapsed tumor had the same outcome as patients with delayed resection (Table 2). A delayed resection was possible in patients with localized relapse ($n = 33$) and in patients with metastatic relapse ($n = 7$).

Outcome after ACCTTIVE and TECC was compared to second-line CHT protocols published in literature (Figure S2).

3.7 | Subgroup analysis of initial high-risk patients

The HR group ($n = 41$) consisted of patients with ARMS ($n = 19$), ERMS ($n = 19$), and spindle-cell RMS ($n = 3$). Comparison of treatment with the CHT regimen ACCTTIVE ($n = 23$) versus TECC ($n = 5$) did not show statistical difference in this subgroup (3-year-OS: 51% ± 29 for ACCTTIVE; 20% ± 35 for TECC; $p = .18$). RT alone or R0/R1 resection did not improve prognosis (Table S4).

4 | DISCUSSION

Pediatric and adolescent patients with localized RMS are reported to have a poor outcome in the majority of patients with a 5-year OS of 21%–37%.[2,24,25] The CWS Guidance included an adapted treatment approach for patients with relapsed disease of RMS considering the initial CHT regimen administered according to the initial risk group. With these recommended regimens, an overall 5-year EFS and OS after diagnosis of relapse of 26% and 31% could be achieved, respectively. Of note, a certain group of patients with initial SR stratification (24% of patients) showed superior outcome with a 5-year OS of 80%, as similarly reported in the ARST0121 study.[1] We confirmed the highly predictive value of TTR and pattern of relapse as previously described,[14] as well as the high impact of the R0/R1 resection in the relapsed setting. Furthermore, the presented data underline the fact that achieving local control by R1 resection with adjacent RT was similar to reaching R0 status by surgery alone.[26,27] Timing of resection in patients with localized relapsed disease was not a prognostic factor in this analysis confirming the current practice: primary resection of the localized disease, if possible, in all other patients the delayed resection is standard of care.

With the present study, we were able to add data on the two second-line regimens ACCTTIVE and TECC to the literature. Treatment with the anthracycline-based ACCTTIVE regimen resulted in a 3-year EFS of 80% in LR/SR patients and 20% in HR patients. These outcomes are comparable to the results reported for the "DCEI regimen" (doxorubicin, carboplatin, etoposide, ifosfamide) used in the ARST0121 study, with 79% 3-year EFS in "favorable-risk" and 17% in "unfavorable-risk" patients.[1,28] Patients of the initial HR/VHR group treated with TECC showed inferior outcome compared to patients of the initial LR/SR group treated with ACCTTIVE, with a 5-year EFS and OS of 10% and 19% confirming reported data.[11] However, these data need to be interpreted with caution as patient numbers are low and not powered to specifically answer this question. Of note, we report an individualized treatment approach rather than a randomized study to add data on possible treatment options in these rare clinical situations.

Response to second-line CHT was not predictive for outcome. However, response imaging was done after cycles 1–5 of therapy, and this variability in response assessment timing is a limitation in interpreting response data. The toxicity and late effects from these regimens are of great interest; however, the lack of more extensive toxicity data is a limitation of this report.

The reported outcome of 24% 2-year EFS in the HR/VHR SoTiSaR cohort is similar to the 2-year EFS of 19% in the VIT cohort excluding patients with refractory disease.[3] Comparing the SoTiSaR data with patients treated within the randomized phase II trial of VIT has several limitations. Overall, the cohort of the randomized phase II trial

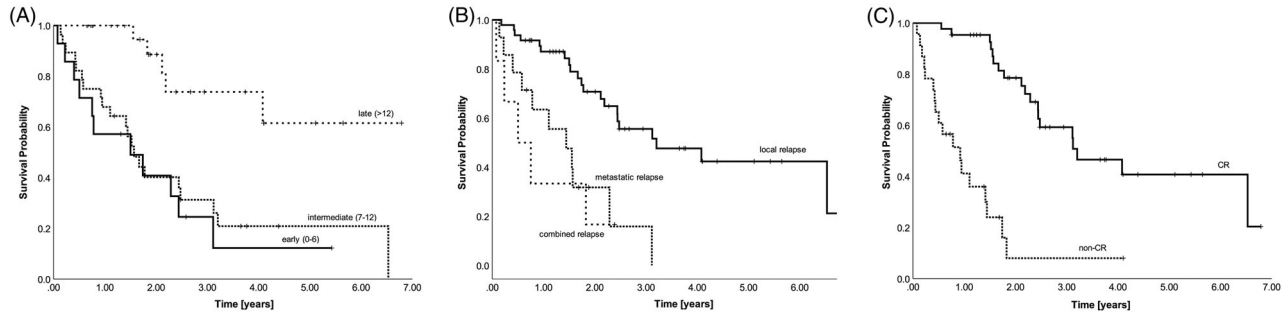

FIGURE 3 Overall survival according to (A) time to relapse (early: $n = 14$; intermediate: $n = 28$; and late: $n = 26$; $p < .001$), (B) type of relapse (local: $n = 48$; metastatic: $n = 14$; combined: $n = 6$; $p < .001$), (C) relapse chemotherapy (ACCTTIVE: $n = 36$; TECC: $n = 12$; other: $n = 15$; and none: $n = 5$), (D) achievement of second complete remission (CR: $n = 43$; non-CR: $n = 23$; unknown: $n = 2$; $p < .001$).

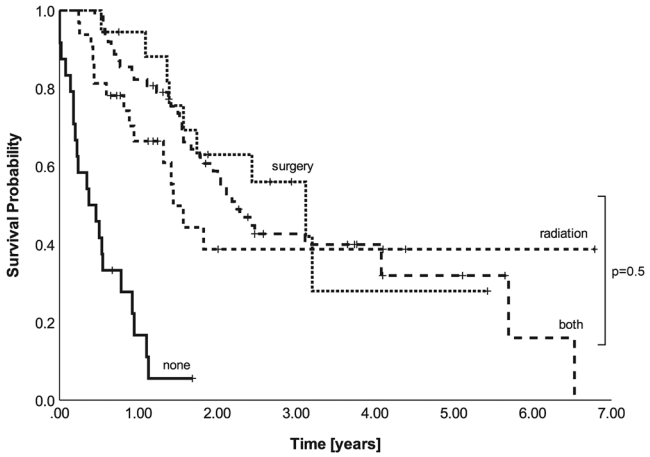

FIGURE 4 Overall survival according to local treatment (surgery: $n = 9$; radiation: $n = 16$; both: $n = 31$; none: $n = 12$). Log-rank test analyzing surgery/radiation/both: $p = .5$. Log-rank test analyzing all patients including patients without local treatment: $p < .001$.

comprises a heterogenous group of heavily pretreated, high-risk patients suffering from more metastatic, second or subsequent relapses and most patients received anthracyclines in the primary treatment. Furthermore, different collectives in and outside randomized studies are difficult to compare.

In conclusion, we confirm long-term survival with multiagent anthracycline-based CHT ACCTTIVE in combination with adequate local control in the subgroup of LR and SR patients with relapsed disease of RMS. International studies including new therapeutic approaches are undoubtedly needed to improve outcome in HR and VHR patients.

AUTHOR CONTRIBUTIONS

Amadeus T. Heinz: data curation, formal analysis, investigation, visualization, and writing—original draft, review, and editing. Martin Ebinger: conceptualization, project administration, supervision, review, and editing. Anton Schönstein: formal analysis, visualization, review, and editing. Jörg Fuchs, Beate Timmermann, Guido Seitz, Marc Münter, Kristian W. Pajtler, Christian P. Kratz, Jochen Rößler, and Gustaf Ljungman: resources, review, and editing. Christian Vokuhl, Sabine Stegmeier, and Thekla von Kalle: investigation, resources, review, and editing. Thomas Klingebiel: methodology, funding, resources, review, and editing. Ewa Koscielniak: conceptualization, funding, methodology, resources, review, and editing. Monika Sparber-Sauer: conceptualization, data curation, methodology, resources, supervision, and writing—original draft, review, and editing.

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CONFLICT OF INTEREST STATEMENT

Monika Sparber-Sauer has acted as consultant and/or advisory board member for Roche, Bayer, and Swedish Orphan Biovitrum (hemophilia). For an independent project on NRKT positive tumors, MSp-S is partially supported by Bayer (Investigation Supported research). None of these disclosures are related to this study.

DATA AVAILABILITY STATEMENT

All data analyzed during the registry are included in this published article (and its supporting files).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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