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Treatment of Pediatric, Adolescent, and Young Adult Patients With Fusion-Positive Alveolar Rhabdomyosarcoma Infiltrating Regional Lymph Nodes in the European CWS-2002P and RMS 2005 Studies and the Soft Tissue Sarcoma Registry

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Keywords: alveolar rhabdomyosarcoma | chemotherapy | fusion-positive rhabdomyosarcoma | local treatment | lymph node involvement | pediatric/adolescent oncology

Abbreviations: ARMS, alveolar rhabdomyosarcoma; CHT, chemotherapy; CI, confidence interval; CR, complete response; CT, computed tomography; CWS, Cooperative Weichteilsarkom Studiengruppe; CYC/VBL, cyclophosphamide/vinblastine; CYC/VNB, cyclophosphamide/vinorelbine; EFS, event-free survival; EpSSG, European Paediatric Soft Tissue Sarcoma Study Group; IRS, Intergroup Rhabdomyosarcoma Study Group; IVA, ifosfamide, vincristine, actinomycin-D; IVADo, ifosfamide, vincristine, actinomycin-D, doxorubicin; LN, lymph node; MRI, magnetic resonance imaging; MT, maintenance treatment; N1, regional lymph node infiltration; OS, overall survival; O-TIE, oral trofosfamide, idarubicine, etoposide; PD, progressive disease; PR, partial response; PT, primary tumor; RMS, rhabdomyosarcoma; RT, radiotherapy; SD, stable disease; SoTiSaR, Soft Tissue Sarcoma Registry; TNM, tumor node metastases; VAC, vincristine, actinomycin-D, cyclophosphamide; VAIA, vincristine, actinomycin-D, ifosfamide, adriamycin.

Monika Sparber-Sauer and Gianni Bisogno contributed equally to this work.

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ABSTRACT

Background: Patients with alveolar rhabdomyosarcoma (ARMS) with regional lymph node involvement (N1) are defined as "very-high-risk rhabdomyosarcoma" in Europe. Different chemotherapy regimens were used in European study protocols.

Methods: Patients with *FOXO1* fusion-positive N1 ARMS registered in the CWS-2002P study, the EpSSG RMS 2005 study, and SoTiSaR were retrospectively investigated. Patients received systemic treatment with chemotherapy (CHT) and local treatment of primary tumor (PT) and involved lymph nodes (LN) with radiotherapy (RT) and/or surgery. Kaplan–Meier estimators and Cox regression were used to examine event-free survival (EFS) and overall survival (OS) according to prognostic factors and treatment.

Results: A total of 156 patients registered in RMS 2005 (n = 99), CWS-2002P (n = 20), and SoTiSaR (n = 37) between 2003 and 2020 were eligible for this analysis. Median age at diagnosis was 10.2 years [0.1–21.9]. Treatment comprised CHT with IVADo (ifosfamide, vincristine, actinomycin-D, doxorubicin, n = 93; 60%), VAIA (vincristine, actinomycin-D, ifosfamide, adriamycin/doxorubicin, n = 53; 34%) or other regimens (n = 10; 6%); resection of the PT (n = 89; 57%), LN sampling or dissection (n = 92; 59%), and/or RT (n = 139; 89%). Maintenance treatment (MT) was added in n = 99/135 (73%) patients who achieved complete remission. Five-year EFS and OS of the cohort were 45% and 47%, respectively. Age and tumor size were independent prognostic factors for EFS. Local treatment applied to the LN with surgery, RT or both significantly improved EFS (p = 0.02) and OS (p = 0.04), with no difference between the modalities (p = 0.7).

Conclusions: Patients with fusion-positive N1 ARMS carry a poor prognosis. Adequate local treatment of LN improved survival.

1 | Introduction

The treatment of localized rhabdomyosarcoma (RMS) is based on risk-adapted treatment schedules, considering known clinical risk factors including histology, primary tumor (PT) site, tumor size, tumor invasiveness, nodal status, and age [1–3].

Recent analyses revealed that the characteristic *PAX3::FOXO1* or *PAX7::FOXO1* fusion gene expressed in most patients with alveolar rhabdomyosarcoma (ARMS) [4] is a better predictor of survival than histology [5, 6]. This was also demonstrated for patients with ARMS and regional lymph node involvement (N1), where fusion-positive ARMS N1 were reported to have a 5-year overall survival (OS) of only 45.5% compared to 74.7% in fusion-negative ARMS N1 [7].

In Europe, all patients with ARMS N1 were defined as "very high risk" (VHR) regardless of fusion status since the 2002 pilot study performed by the Cooperative Weichteilsarkom Studiengruppe (CWS-2002P) demonstrated a poor prognosis for this group of patients [8]. European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) and CWS decided to treat these patients with an intensive initial chemotherapy (CHT), followed by maintenance CHT based on the promising results achieved in metastatic RMS [9]. The overall treatment strategy was similar in the different trials, but there were differences in the use of doxorubicin in the initial CHT and in the choice of agents for the maintenance regimens.

In this pooled analysis of EpSSG and CWS data, treatment and outcome of 156 patients with fusion-positive ARMS N1 included in the trials CWS-2002P, RMS 2005, and the Soft Tissue Sarcoma Registry (SoTiSaR) from 2003 to 2020 are reviewed with the aim of comparing the results of different treatment concepts in a homogenously defined cohort.

2 | Methods

2.1 | Patients

EpSSG RMS 2005 (*NCT* 00379457), CWS-2002P [8], and SoTiSaR [10–12] included patients with a histopathologically proven diagnosis of RMS who were 0–21 years of age (0.5–21 years for RMS 2005).

All patients with fusion-positive ARMS and regional lymph node (LN) infiltration, without distant metastases, diagnosed between 2003 and 2020 with follow-up until December 2021, were included in the current analysis.

2.2 | Definition of Terms

The diagnostic workup included magnetic resonance imaging (MRI) and/or computed tomography (CT) of the PT and regional LN. PT site was assigned to one of the location groups as previously defined: orbital, head/neck non-parameningeal and genitourinary non-bladder-prostate, which were considered as favorable sites in contrast to the so-called unfavorable sites: head/neck parameningeal, genitourinary bladder-prostate, extremities and "other" (e.g., abdominal or thoracic) [13].

Regional LNs were defined as those draining the site of the PT [7]. In case of distant LN or other metastases, patients were not eligible for this analysis. In RMS 2005, surgical examination of regional LN was strongly advised for RMS located in the extremities regardless of clinical or radiological status, and recommended for suspicious nodes at PT sites apart from the limbs [7]. In CWS-2002P and CWS Guidance, routine biopsy or LN sampling was not required, but was recommended for clinically and radiologically suspicious regional LN [8].

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The staging system used was adapted from the Intergroup Rhabdomyosarcoma Study Group (IRS) classification [14] and the tumor node metastases (TNM) classification [15–18]. Surgical margins were defined at the time of pathological assessment. Resection margins after primary or delayed surgery of the PT were classified as microscopically complete (R0), macroscopically complete (R1), or macroscopically incomplete (R2) [19]. Secondary surgery was defined as a delayed surgical approach after CHT. Best surgery of the PT was defined as the best surgical result of the sum of all resections [20]. Local control was defined as any surgical resection and/or irradiation applied to the PT and/or nodes.

Response of PT and regional LNs was assessed after 9 weeks of initial CHT in all trials. Complete response (CR) was defined radiologically by complete disappearance of disease. Minor partial response (mPR) was defined as greater than or equal to one-third tumor volume reduction and partial response (PR) as greater than or equal to two-third volume reduction, mainly reflecting the response of the PT. Progressive disease (PD) was defined in CWS-2002P [8] and CWS Guidance [21] as any increase in tumor volume of PT or LN or appearance of new lesions in patients who had not achieved prior CR, in RMS 2005 [22, 23] as increase of tumor volume by 40% or appearance of new lesions. Stable disease (SD) was defined as any response not fulfilling the criteria for (m)PR or PD. For the purpose of this analysis, the definitions of RMS 2005 were applied to all patients, with mPR and PR pooled together into one group.

Relapsed disease was defined as any new tumor appearance after having achieved CR. Local relapse was defined as reoccurrence of the PT at the original tumor site, with or without LN infiltration. Nodal relapse was defined as isolated reoccurrence of regional LN infiltration. A metastatic relapse was seen as the appearance of new metastatic lesions distant to the PT site and directly adjacent tissues. Relapses at both local and metastatic sites were defined as combined relapses.

2.3 | Treatment

All patients received multimodal treatment with CHT and, if feasible, local therapy of PT and regional LNs in the form of surgery and/or radiotherapy (RT).

Local treatment with RT and/or delayed resection was recommended no later than after the fourth CHT course [8, 23]. External beam RT was scheduled to be given to the PT in all patients above 1 year of age, with doses ranging from 41.4 to 50.4 Gy (± optional tumor boost) according to the type of resection and response to CHT (Table S1). In patients below 1 year, RT was applied based on investigators discretion according to the study protocol in EpSSG RMS 2005 and CWS-2002P and based on physician's discretion in SoTiSaR. RT to regional LNs was recommended for all patients, with 44.8 Gy in CWS-2002P and 41.4 Gy (+9 Gy boost in patients with macroscopic residual disease) in RMS 2005/CWS Guidance. LN dissection was not recommended, except in the very young patients who could not receive RT. In the CWS and EpSSG databases, "surgery of LN" did not differentiate between radical LN dissection and non-extensive sampling of a single LN. "Surgery of LN" was performed at diagnosis and/or after neoadjuvant CHT. For the purpose of this analysis, all LN surgeries (if any) are summarized as noted in the dataset.

For CHT, VAIA (vincristine, actinomycin-D, ifosfamide, adriamycin/doxorubicin) [24] was scheduled for VHR patients in CWS-2002P and CWS Guidance, with the full treatment schedule depicted in Figure S1. Induction CHT in RMS 2005 relied on IVADo/IVA (ifosfamide, vincristine, actinomycin-D, doxorubicin/ifosfamide, vincristine, actinomycin-D) (the following: IVADo) chemotherapy for VHR patients [7, 25, 26]. The main difference between VAIA and IVADo lies in the distribution and total dose of doxorubicin and actinomycin-D, as displayed in Figure S1: doxorubicin and actinomycin-D alternate in VAIA cycles, whereas in IVADo, doxorubicin is dose intense applied in the first four consecutive cycles, and actinomycin-D is scheduled for every treatment course. In EpSSG RMS 2005, the planned cumulative dose of doxorubicin and maximum cumulative dose of actinomycin-D were 240 and 13.5 mg/m^2, respectively, compared to maximum cumulative doses of 320 mg/m^2 doxorubicin and 7.5 mg/m^2 actinomycin-D in the CWS trials. As most patients received irradiation, omitting or postponing the fourth doxorubicin dose in VAIA and/or actinomycin-D doses during RT was frequent, as indicated in Figure S1.

Intensive CHT was followed by six 4-weekly cycles of low-dose, metronomic maintenance treatment (MT) with cyclophosphamide and vinblastine (CYC/VBL) in CWS-2002P [8]. Based on the results of a pilot study combining cyclophosphamide and vinorelbine (CYC/VNB) [27], the EpSSG used this regimen in the RMS 2005 trial [22]. Patients registered in SoTiSaR could be included in the CWS-2007 HR trial, which randomized no MT versus MT with trofosfamide, idarubicin, and etoposide (O-TIE) [9, 28] for 6 months after induction CHT (Figure S1). O-TIE was also administered as individual decision of the treating center.

2.4 | Data Collection and Evaluation

Written informed consent for data collection from the patient or from their legal guardians, or both, was required for all patients enrolled in the trials RMS 2005, CWS-2002P, and SoTiSaR. All trials were performed per requirements of the declaration of Helsinki and in accordance with the approval of the respective ethical committee. In addition to the data available in the databases obtained by yearly status reports, medical reports of CWS patients were studied by the first author.

2.5 | Statistical Methods

Statistical analyses were conducted using SPSS 27 and RStudio 2022.12.0. OS and event-free survival (EFS) were calculated using the Kaplan–Meier estimator [29], and with confidence intervals (CI) stated at the 95% level. For OS, the time from diagnosis to death, or last follow-up was calculated. For EFS, the time from diagnosis to progression, relapse after CR, diagnosis of secondary malignancy, death or last follow-up was calculated. 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

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5 years. Cox proportional hazards regression model was used to simultaneously assess the effect of prognostic factors on EFS and OS. The proportional hazards assumption was examined by checking Schoenfeld residuals. Post-relapse OS of patients was calculated from the time of diagnosis of relapsed or PD to second progression, second relapse, death, or last follow-up, respectively. All statistical tests were conducted at $\alpha = 0.05$. Following conventions, statistically significant results are marked with an asterisk (*) when they reach $p < 0.05$ and with (**) when they reach $p < 0.001$. The research is exploratory, and hence the sample sizes are not powered for each examined endpoint. In cases with a low number of events, this can indeed increase type II errors; however, in any case a nonsignificant *p*-value does not mean that equality was proven but much more that a difference could not be shown. Descriptive statistics are reported as median [range], if not otherwise specified.

3 | Results

3.1 | Patient Characteristics and Demography

Overall, 1733 patients with localized RMS entered into the EpSSG RMS 2005 trial and 1207 into CWS-2002P/SoTiSaR. Out of these patients, $n = 99$ (5.7%) from RMS 2005, $n = 20$ from CWS-2002P, and $n = 37$ from SoTiSaR (4.7%) with fusion-positive ARMS, nodal infiltration, and complete clinical dataset were identified, totaling to 156 patients eligible for this analysis (Table 1).

Median age at diagnosis was 10.2 years [0.1–21.9 years]. Median follow-up was 4.3 years [0.4–13.9 years] from diagnosis and 1.3 years [0–6.5 years] after relapse. A fusion involving the *PAX3* gene was the most frequent translocation found ($n = 104/156$, 65%, Table 1). Most patients were diagnosed with large tumors greater than 5 cm ($n = 103/149$, 69%, $n = 7$ unknown), infiltrating the surrounding tissues (T2, $n = 100/151$, 66%, $n = 5$ unknown) and arising in unfavorable PT sites ($n = 128/156$, 82%). Except for more T2 tumors in the CWS cohort, there were no significant differences in initial clinical characteristics between the EpSSG and CWS patient cohorts (Table S2).

3.2 | Treatment

After tumor biopsy or upfront tumor resection, patients were classified as IRS II ($n = 7/156$, 4%) or IRS III ($n = 149/156$, 96%). CHT was given to all patients: IVADo ($n = 93/156$, 60%) and VAIA ($n = 53/156$, 34%) according to protocol (Table 2). Ten patients received other regimens: IVA was given to five patients, VAC to one patient (cyclophosphamide, vincristine, actinomycin-D), and four patients were included into the CWS-IV 2002 trial [30], where topotecan and carboplatin were added to VAIA.

Among 149 IRS III patients, response to CHT was CR in $n = 11$ (7%), PR in $n = 98$ (66%), SD in $n = 2$ (1%), and PD in $n = 2$ (1%), not evaluable in 36 patients (23%). No differences in response rates between IVADo and VAIA were found (CR in 10/11% of evaluable patients, PR in 86/86%, SD in 3/0%, PD in 1/3%).

Delayed resection of the PT was performed in $n = 69/156$ (44%), including re-resection after initial surgery of the PT in $n = 3$ patients, leading to a total of 89 patients who underwent surgery of the PT at any time. Result of best surgery was R0 ($n = 53/89$, 60%), R1 ($n = 18/89$, 20%), and R2 ($n = 18/89$, 20%). RT was applied to the PT after delayed surgery in $n = 72$ (46%), definitive RT without surgery was administered in $n = 64$ (41%) patients. Median total dose applied to the PT in CWS-2002P was 45.9 Gy [44–60], versus 50.4 Gy [35.2–59.4] in RMS 2005 and 50.5 Gy [41.1–59.4] in patients registered within SoTiSaR. Infants below 1 year of age ($n = 6$) underwent PT resection alone ($n = 3/6$, 50%), combined with RT ($n = 1$), received definitive RT ($n = 1$), or no treatment of PT ($n = 1$).

Local treatment of regional LN consisted of surgery (sampling or dissection, $n = 30/156$; 19%), RT ($n = 46/156$; 29%), or surgery and RT ($n = 62/156$; 40%). A direct comparison of local treatment between EpSSG and CWS (Table S2) showed that patients enrolled in RMS 2005 had a significantly higher rate of delayed R0 resections (76% vs. 34%) and a higher rate of LN irradiation (92% vs. 53%) compared to CWS patients who received at a higher rate of LN sampling or dissection as the only local treatment to the nodes (EpSSG 9% vs. CWS 37%). Local treatment of regional LN in infants less than 1 year consisted of surgery alone ($n = 2$), surgery + RT ($n = 1$), definitive RT ($n = 1$), or no local treatment ($n = 2$).

Maintenance CHT with CYC/VNB after induction CHT was given to 85 RMS 2005 patients ($n = 77$ in CR, $n = 8$ in non-CR) and with CYC/VBL to 14 CWS-2002P patients ($n = 13$ in CR, $n = 1$ in non-CR). Ten patients received O-TIE ($n = 9$ in CR, $n = 1$ in non-CR). CR was achieved in 135/156 (87%) patients.

3.3 | Overall Outcome and Prognostic Factors

The overall 5-year EFS and OS for all 156 patients were 45% [95% CI: 37–53] and 47% [95% CI: 39–56], respectively (Figure 1). The three different patient cohorts treated within the CWS-2002P and RMS 2005 studies and registered within SoTiSaR showed comparable outcomes (Table 1). Unfavorable age at diagnosis (<1 or ≥10 vs. 1–10 years, $p = 0.05$), translocation partner (*FOXO1* break positive, unknown translocation partner vs. *PAX3/7::FOXO1* fusion, $p = 0.018$), unfavorable tumor site ($p = 0.04$, Table 1), and large tumor size (>5 vs. ≤5 cm, $p = 0.04$) were significantly correlated with inferior survival (Figure S2). Multivariate Cox regression analysis confirmed age less than 1 year (hazard ratio [HR]: 5.2 [1.9–14], $p < 0.001$) and tumor size greater than 5 cm (HR 2.1 [1.1–3.8], $p = 0.021$) as independent risk factors for EFS (Table 3). Age less than 1 year also significantly increased the HR for death ($p < 0.001$), whereas tumor size greater than 5 cm missed statistical significance for OS (HR 1.67 [0.91–3.1], $p = 0.1$). Fusion status was not included in the multivariate analysis.

Local control of the PT and regional LN with surgery or RT and attainment of CR at the end of treatment were associated with superior survival (Table 2). There was no statistical evidence indicating a difference in outcome for EFS ($p = 0.7$) or OS ($p = 0.7$) between surgery, irradiation, or both modalities for local treatment of LN (Table 2, Figure 2). Irradiation of regional LNs was combined with RT of the PT in all but three cases.

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TABLE 1 | Univariate analysis of disease characteristics in $n = 156$ patients with fusion-positive N1 ARMS.

Characteristic	$N = 156$[a]	5-year EFS (95% CI)	p-value[b]	5-year OS (95% CI)	p-value[b]
Patient cohort			0.5		>0.9
CWS-2002P	20 (13%)	50% [32%, 78%]		48% [30%, 77%]	
SoTiSaR	37 (24%)	40% [26%, 62%]		49% [34%, 72%]	
RMS 2005	99 (63%)	45% [36%, 56%]		46% [37%, 58%]	
Gender			0.7		0.5
Female	70 (45%)	46% [35%, 60%]		50% [38%, 65%]	
Male	86 (55%)	44% [34%, 56%]		45% [35%, 57%]	
Age			0.15		0.05[c]
<1 year	6 (4%)	33% [11%, 100%]		33% [11%, 100%]	
≥1 to <10 years	70 (45%)	51% [40%, 64%]		54% [42%, 68%]	
≥10 years	80 (51%)	40% [31%, 53%]		42% [32%, 56%]	
Fusion status			0.10		0.018[c]
FOXO1 break	38 (24%)	28% [16%, 49%]		29% [17%, 50%]	
PAX3::FOXO1[c]	104 (65%)	51% [42%, 62%]		53% [43%, 64%]	
PAX7::FOXO1	14 (9%)	39% [20%, 77%]		53% [31%, 89%]	
PT size			0.008[c]		0.04[c]
≤5 cm	46 (31%)	64% [51%, 80%]		61% [47%, 78%]	
>5 cm	103 (69%)	36% [27%, 47%]		42% [33%, 53%]	
Unknown	7				
T status			0.2		0.12
T1	51 (34%)	50% [37%, 66%]		54% [40%, 71%]	
T2	100 (66%)	43% [34%, 54%]		43% [34%, 55%]	
Unknown	5				
PT site			0.3		0.4
EXT	51 (33%)	36% [25%, 53%]		40% [28%, 59%]	
HN-nPM	25 (16%)	59% [43%, 82%]		68% [51%, 89%]	
HN-PM	45 (29%)	43% [31%, 61%]		43% [30%, 62%]	
UG	8 (5%)	50% [25%, 100%]		40% [15%, 100%]	
OTH	27 (17%)	46% [30%, 71%]		45% [28%, 70%]	
PT site risk			0.09		0.04[c]
Favorable	28 (18%)	60% [44%, 82%]		67% [51%, 87%]	
Unfavorable	128 (82%)	41% [33%, 51%]		42% [34%, 53%]	
IRS stage			0.6		0.14
II	7 (4%)	67% [38%, 100%]		80% [52%, 100%]	
III	149 (96%)	44% [36%, 53%]		46% [38%, 55%]	

Abbreviations: EXT, extremities; HN-(n)PM, head and neck (non-)parameningeal; IRS, Intergroup Rhabdomyosarcoma Study; OTH, other; PT, primary tumor; UG, urogenital.

[a] n (%).

[b] Log-rank test.

[c] Including $n = 2$ PAX3::NCOA-positive ARMS.

When comparing the different CHT regimens, outcome in the subgroup of patients receiving IVADo without MT and patients receiving VAIA+O-TIE was significantly worse compared to IVADo+CYC/VNB, VAIA, or VAIA+CYC/VBL (5-year OS 20% [95% CI: 8–52] vs. 53% [95% CI: 44–64], $p = 0.003$, Figure 3A). Detailed investigation showed that local treatment (surgery and/or RT) of the PT of LN was performed less frequently in the IVADo/VAIA+O-TIE cohort, and CR at the end of treatment was achieved less often (Table S3). When comparing only patients who achieved CR, the difference between both cohorts

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TABLE 2 | Univariate analysis of treatment in $n = 156$ patients with fusion-positive N1 ARMS.

Characteristic	$N = 156$[a]	5-year EFS (95% CI)	p-value[b]	5-year OS (95% CI)	p-value[b]
Initial surgery of primary tumor			0.4		0.3
No	133 (85%)	42% [35%, 52%]		45% [36%, 55%]	
Yes	23 (15%)	59% [41%, 84%]		59% [41%, 86%]	
Delayed surgery of primary tumor			0.4		0.3
No	87 (56%)	51% [41%, 63%]		54% [44%, 66%]	
Yes	69 (44%)	36% [25%, 50%]		38% [27%, 53%]	
Resection of primary tumor any time			0.6		0.6
No	67 (43%)	50% [39%, 63%]		53% [41%, 67%]	
Yes	89 (57%)	40% [31%, 53%]		42% [32%, 55%]	
Best surgery or primary tumor			0.067		0.12
R0	53 (60%)	45% [33%, 62%]		49% [36%, 67%]	
R1	18 (20%)	30% [14%, 62%]		29% [14%, 61%]	
R2	18 (20%)	35% [18%, 69%]		35% [18%, 70%]	
Local control of primary tumor			<0.001**		<0.001**
No	3 (2%)	— (—, —)		— (—, —)	
Surgery and/or RTX	153 (98%)	45% [38%, 54%]		48% [40%, 57%]	
Local control of lymph nodes			0.019*		0.040*
No	18 (11%)	28% [13%, 59%]		32% [16%, 64%]	
Surgery and/or RTX	138 (88%)	47% [39%, 56%]		49% [41%, 59%]	
Regional lymph node treatment					
Surgery only	30 (22%)	44% [29%, 67%]	0.7	54% [38%, 76%]	0.7
RT only	46 (33%)	54% [40%, 72%]		56% [42%, 74%]	
Surgery and RT	62 (45%)	43% [33%, 58%]		41% [30%, 57%]	
No local treatment of nodes			18		
RT of primary tumor and/or lymph nodes			0.059		0.2
No	17 (11%)	28% [13%, 62%]		33% [16%, 66%]	
Yes	139 (89%)	47% [39%, 56%]		49% [40%, 59%]	
Site of radiation			0.059		0.037*
Primary tumor	31 (22%)	43% [28%, 65%]		53% [38%, 74%]	
Nodes	3 (2%)	— (—, —)		— (—, —)	
Primary tumor + nodes	105 (76%)	49% [40%, 60%]		49% [40%, 61%]	
Chemotherapy and MT			<0.001**		0.003*
IVADo+CYC-VNB	81 (55%)	51% [41%, 64%]		52% [42%, 65%]	0.4
VAIA	32 (22%)	40% [25%, 65%]		49% [32%, 73%]	
VAIA+CYC-VBL	13 (9%)	69% [48%, 99%]		69% [48%, 99%]	
VAIA+O-TIE	8 (6%)	— (—, —)		— (—, —)	0.3
IVADo	12 (8%)	17% [4.7%, 59%]		17% [4.7%, 59%]	
Maintenance treatment			<0.001**		0.02*
No maintenance	47 (30%)	33% [22%, 52%]		38% [25%, 57%]	
CYC-VNB/CYC-VBL	99 (63%)	52% [43%, 63%]		53% [44%, 65%]	
O-TIE	10 (7%)	— (—, —)		— (—, —)	

(Continues)

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TABLE 2 | (Continued)

Characteristic	$N = 156$[a]	5-year EFS (95% CI)	p-value[b]	5-year OS (95% CI)	p-value[b]
Response to CHT			0.5		0.6
CR	11 (11%)	62% [39%, 100%]		61% [37%, 100%]	
PR	98 (89%)	46% [37%, 57%]		48% [39%, 60%]	
1st CR			<0.001**		<0.001**
No	21 (13%)	4.8% [0.7%, 32%]		4.8% [0.7%, 32%]	
Yes	135 (87%)	51% [43%, 61%]		54% [45%, 64%]	

Abbreviations: CHT, chemotherapy; CR, complete response; CYC-VBL, cyclophosphamide, vinblastine; CYC-VNR, cyclophosphamide, vinorelbine; IVADo, ifosfamide, vincristine, actinomycin-D, doxorubicin; O-TIE, oral trofosfamide, idarubicin, etoposide; PR, partial response; PT, primary tumor; RTX, radiotherapy; VAIA, vincristine, ifosfamide, actinomycin-D, doxorubicin.

[a] n (%).

[b] Log-rank test.

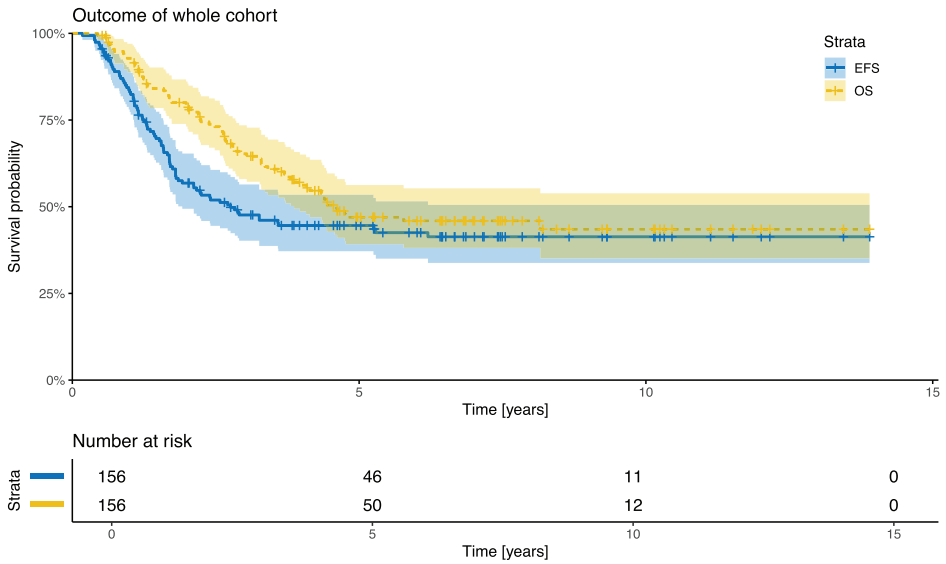

FIGURE 1 | Event-free and overall survival for the whole cohort investigated ($n = 156$).

narrowly misses statistical significance (5-year OS 31% [95% CI: 13–76] for IVADo or VAIA+O-TIE vs. 58% [95% CI: 49–69] for IVADo+CYC/VNB, VAIA, or VAIA+CYC/VBL, $p = 0.08$).

Maintenance treatment with CYC/VNB or CYC/VBL was associated with improved 5-year EFS ($p < 0.001$) and OS ($p = 0.02$) compared to O-TIE or no maintenance (Table 2, Figure 3B), without a statistically significant difference between the CYC/VNB and the CYC/VBL regimen regarding EFS ($p = 0.34$) and OS ($p = 0.4$). When excluding patients with non-CR or O-TIE MT, no statistically significant difference in 5-year EFS between CYC/VNB or -VBL MT (58% [95% CI: 48–70], $n = 90$) versus no MT (52% [95% CI: 37–74], $n = 36$, $p = 0.3$) was reached.

3.4 | Relapsed or Refractory Disease

An event occurred in $n = 86/156$ (55%) patients that could be classified as relapse ($n = 67/86$, 78%), progression ($n = 15/86$, 17%), secondary malignancy ($n = 3$), or death due to unknown reason ($n = 1$, Table S4). Median time from initial diagnosis to event was 18.2 months [2–63]. Most relapses occurred as metastatic or combined relapse (64% of all relapses), whereas PD had an equal distribution between local (50%) or metastatic/combined progression (50%). Isolated nodal relapse occurred more frequently in CWS-2002P ($n = 2/10$, 20%) or SoTiSaR ($n = 4/16$, 25%) compared to RMS 2005 (6/54, 11%), whereas local failures were more common in RMS 2005 ($n = 16/54$, 30%). There was no significant difference in relapse pattern distinguishing between the subgroups undergoing LN surgery (local/nodal/metastatic relapse: 13%/20%/66% of events), LN irradiation (30%/15%/55% of events), or LN sampling/dissection+RT (15%/15%/70% of events, Fisher's exact test: $p = 0.8$). Three-year post-relapse survival was dismal at only 12% [95% CI: 4.6%–19%] in relapsed disease and 0% in primary PD.

4 | Discussion

With this pooled analysis of patients with fusion- and nodal-positive ARMS, we can report a 5-year EFS and OS of 45% [95% CI: 37–53] and 47% [95% CI: 39–56], showing the absence of a "salvage gap" [31] as most patients succumbed to their disease after failure of first-line treatment.

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TABLE 3 | Multivariable analysis of EFS and OS in $n = 145$ patients with 78 events.

EFS			
Covariate[a]	**HR**	**95% CI [lower, upper]**	***p*-value**
Age			
1–9 years	Reference		
<1 year	5.2	[1.9, 14.30]	0.001**
≥10 years	1.29	[0.80, 2.07]	0.294
PT site (unfavorable vs. favorable)	1.37	[0.66, 2.86]	0.397
PT size (>5 vs. ≤5 cm)	2.05	[1.11, 3.76]	0.021*
T status (T2 vs. T1)	1.45	[0.87, 2.39]	0.152
OS			
Covariate[a]	**HR**	**95% CI [lower, upper]**	***p*-value**
Age			
1–9 years	Reference		
<1 year	5.66	[2.05, 15.61]	0.001***
≥10 years	1.47	[0.89, 2.44]	0.135
PT site (unfavorable vs. favorable)	1.75	[0.78, 3.94]	0.174
PT size (>5 vs. ≤5 cm)	1.67	[0.91, 3.07]	0.098
T status (T2 vs. T1)	1.54	[0.90, 2.64]	0.114

Note: 11 Observations excluded due to missing values for covariate data.

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival; PT, primary tumor.

[a]Fusion status not included, as PAX3::FOXO1 vs. PAX7::FOXO1 fusion status was not predictive in the univariate analysis, and the subgroup of FOXO1 break-positive patients was poorly defined (see Discussion).

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

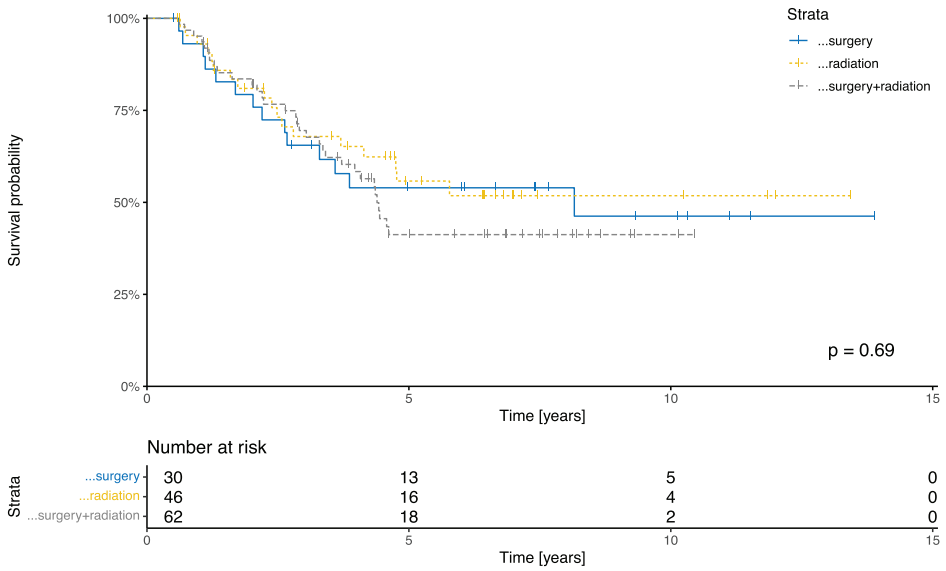

FIGURE 2 | Overall survival dependent on which treatment was applied to regional lymph nodes: surgery ($n = 30$), radiation ($n = 46$), or both ($n = 62$).

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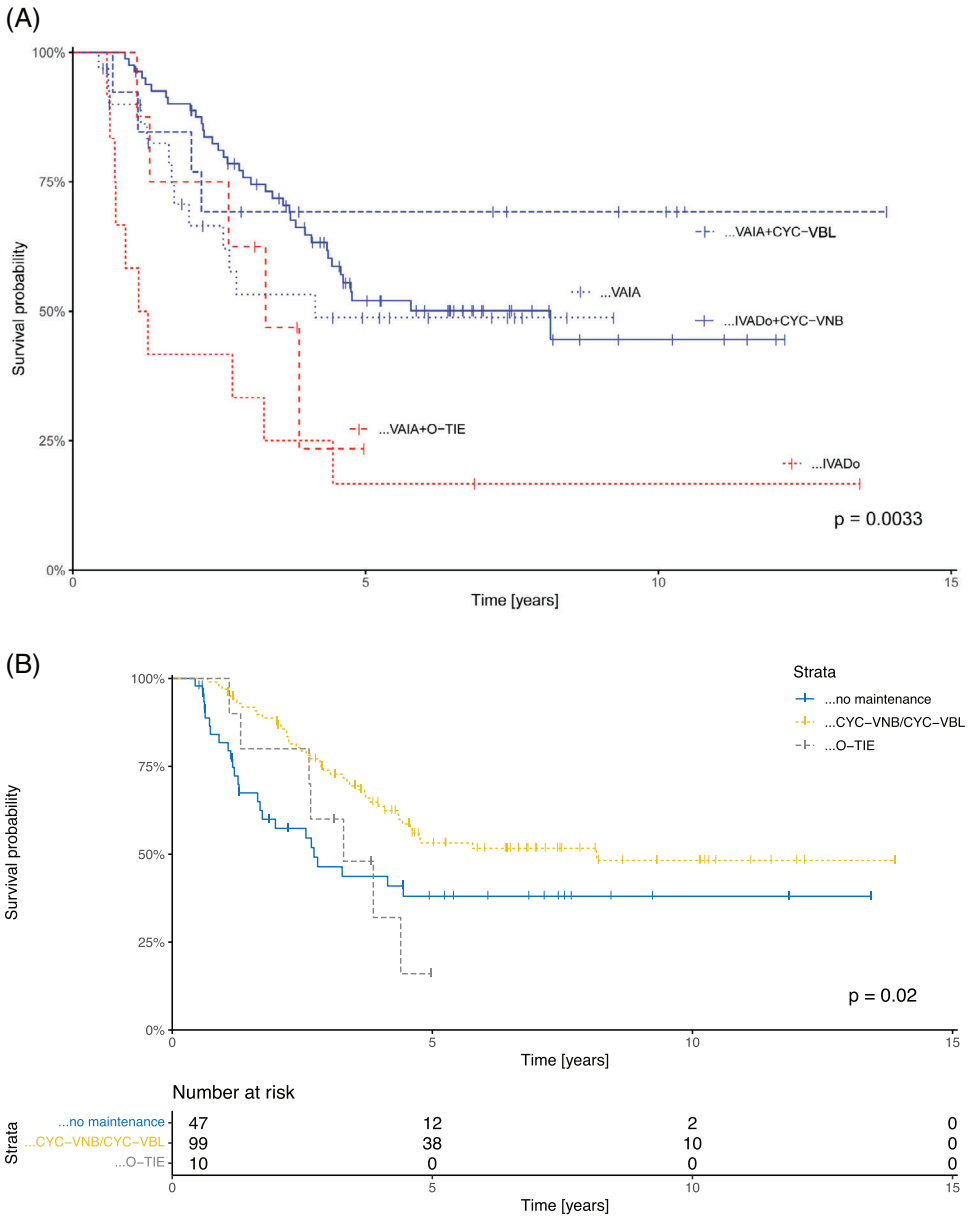

FIGURE 3 | Overall survival of the investigated cohort according to: (A) chemotherapy regimen applied (IVADo: ifosfamide, vincristine, actinomycin-D, doxorubicin; VAIA: vincristine, actinomycin-D, ifosfamide, adriamycin/doxorubicin; CYC/VNB: cyclophosphamide, vinorelbine; CYC/VBL: cyclophosphamide, vinblastine; O-TIE: oral trofosfamide, idarubicin, etoposide); (B) maintenance treatment applied.

We confirm the prognostic value of age, tumor site, and tumor size for OS as previously shown for localized RMS [1–3], but in contrast to the recent findings in ARMS N1 (including fusion-negative ARMS) [7], tumor invasiveness was not significantly correlated with inferior outcome in our cohort. Analogous to recently published results [32], age, and tumor size were the only independent risk factors for EFS. For OS, only age below 1 year was significantly increasing the risk for death. The limitations of local treatment in infants below 1 year of age [33, 34], especially concerning lower rates of RT compared to older patients as shown by our analysis, might contribute to the inferior outcome. Adolescent age greater than 10 years showed a tendency of inferior EFS and OS in this highly selected subgroup of fusion-positive ARMS N1 patients, but this tendency was not significant in the multivariate analysis. This indicates that fusion-positive ARMS is a homogenous subgroup across a wide age spectrum, in contrast to fusion-negative ERMS where adolescent versus young age was a highly predictive risk factor in localized as well as metastatic disease [1].

As N0 ARMS were not included in our analysis, future studies are needed to definitely classify N1 fusion-positive ARMS as “very high risk” or “high risk” [8].

Lastly, fusion status was not included into the Cox regression model, as PAX3 versus PAX7 fusion status was not predictive for outcome in the univariate analysis. The subgroup of FOXO1 break-positive patients showing inferior survival was poorly defined, taking together patients in whom the FOXO1 break was confirmed by FISH without subsequent RT-PCR or RNA sequencing for identifying the translocation partner, as well as an unknown number of patients

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who might had other, rare translocations (e.g., PAX3-NCOA) [35].

However, this analysis contributes a detailed investigation of treatment results in the specific subgroup of fusion-positive ARMS to the literature, and we demonstrated that the overall outcome in all three patient cohorts (CWS-2002P, EpSSG RMS 2005, SoTiSaR) was identical despite differences in induction and maintenance treatment. The authors recommend a future common European standard treatment with IVADo, which gave the same OS compared to patients treated with VAIA but lower cumulative doses of anthracyclines.

Interestingly, the 4-year EFS and OS (48.6% and 56.4%, respectively) for fusion-positive ARMS N1 reported in a large COG series [32] were strikingly similar to our results for 5-year EFS and OS. However, the COG outcomes were achieved without doxorubicin or prolonged maintenance therapy. Future studies are needed on the role of doxorubicin in this patient cohort, especially in light of the negative results seen in the randomized dose intensification with doxorubicin for high-risk RMS in EpSSG RMS 2005 [23]. The ongoing FaR-RMS trial (EudraCT 2018-000515-24) includes the randomization of the regimen IVADo versus IrIVA (irinotecan, ifosfamide, vincristine, dactinomycin) and might help clarifying this question.

In addition, we revealed that local treatment of regional LN seems to be associated with improved survival, in contrast to published findings for fusion-negative ERMS N1 [36]. Interestingly, most patients not undergoing local treatment of regional LN did receive resection and/or irradiation of the PT, indicating that early PD cannot explain why these patients were missing adequate LN treatment according to protocol recommendations.

As a limitation, the underlying dataset did not clearly distinguish between LN sampling and radical dissection. This might explain that the 40% of patients undergoing "surgery and RT" to the regional LN probably received sampling of selected LN with adjuvant RT of the whole LN draining area. Analyzing this patient cohort, considering the time point of LN surgery would be of interest in differentiating the leading effects in patients receiving both modalities. However, as a limitation of a retrospective European analysis, no detailed data were available on timing of LN surgery.

Of note, patients treated according to CWS protocols received less LN irradiation than patients treated according to the EpSSG protocol even though the RT guidelines were similar. This might be due to the fact that for patients outside clinical trials (SoTiSaR) individual treatment options were also performed. Nevertheless, our data did not reveal a clear advantage of a specific treatment modality over the other, analogous to data of the Children's Oncology Group (COG) in paratesticular RMS [37]. The variation of management of LN metastases in EpSSG and CWS protocols and the smaller number of patients receiving maintenance CHT in the latter group show that a subset of patients might be undertreated. This might be attributed to the lack of radiation therapy to involved LNs rather than the advantage of maintenance CHT, but is not proven.

Delayed primary excision achieving R0 status was not improving EFS and relapsed disease was mostly metastatic, reflecting the aggressive biological behavior of fusion-positive RMS disease and the difficulty of achieving control of the overall disease through local control. This might also explain why outcome of patients treated in RMS 2005 was not better than in CWS 2002P/SoTiSaR, despite striking differences in the rate of R0 resected patients. Another possible explanation for the high rate of R0 resected patients in RMS 2005 might be that surgical margins have potentially been described divergently between different EpSSG and different CWS treatment centers [38], despite the definitions in the EpSSG and CWS protocols were equal.

Another main message of this analysis is the role of MT: maintenance treatment with CYC/VNB or CYC/VBL seemed to be associated with improved 5-year EFS and OS compared to O-TIE or no maintenance treatment in this analysis with no difference between the CYC/VNB and the CYC/VBL regimens. As the analysis of maintenance treatment in this retrospective cohort might be exposed to a selection bias toward patients not suffering from primary refractory disease before start of maintenance treatment [39], a subgroup analysis was performed only comparing patients in CR and excluding the small subgroup of O-TIE patients. Here, the benefit of CYC/VNB or -VBL MT versus no maintenance could not be demonstrated. Also, the 5-year OS of 53% in our subgroup of patients receiving CYC/VNB or -VBL MT is nearly identical to the 53.7% reported by COG for fusion-positive RMS N1 [40], where patients received a prolonged VAC schedule (42 weeks), but no MT. In our cohort, median time to event was 18 months, meaning that most relapses occurred after the end of the recent 6-month induction + 6-month MT schedule. It will be therefore of great interest to see if the prolonged MT (randomized between 12 vs. 24 months) in the ongoing FaR-RMS trial (EudraCT 2018-000515-24) has an impact on survival. In conclusion, this pooled analysis of patients with fusion-positive ARMS N1 treated according to different protocols revealed similar outcome despite minor differences in systemic treatment approach. One future common European treatment strategy with the regimen IVADo, MT with CYC/VBL, and local treatment of the PT and regional LNs with surgery and/or irradiation is reasonable and future focus on European phase I/II studies including personalized therapy are urgently necessary.

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Conflicts of Interest

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 NTRK-positive tumors, Monika Sparber-Sauer is partially supported by Bayer (investigation supported research). Anton Schönstein is now an employee of Boehringer Ingelheim. None

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of these disclosures are related to this study. Hans Merks has acted as a consultant and/or advisory board member for Merck, GlaxoSmithKline, and Bayer.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

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