European Journal of Surgical Oncology 52 (2026) 110535

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Number of affected lymph nodes predicts outcome in extremity rhabdomyosarcoma

Luna Margotte [a], Anton Henssen [a], Anne Thorwarth [a], Angelika Eggert [a,c], Monika Scheer [a,b,*]

[a] Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Pediatric Hematology and Oncology, Augustenburger Platz 1, 13353, Berlin, Germany
[b] Pediatrics III, West German Cancer Center, University Hospital Essen, Essen, Germany
[c] University Hospital Essen, Essen, Germany

ARTICLE INFO

Keywords:
Soft tissue sarcoma
Rhabdomyosarcoma
Extremity
Lymph node
Prognostic factors
Risk stratification
Cross-age study
Population-based
Site of metastases

ABSTRACT

Background: Rhabdomyosarcoma (RMS) of the extremity has poor outcomes due to its high potential for lymphatic and haematogenic spread.
Methods: Data were selected from the SEER17 registry 2000–2020 for non-pleomorphic extremity rhabdomyosarcoma (all ages and stages).
Results: 473 cases were identified, 181 at upper and 292 at lower extremity. Median age was 14years. Histology was alveolar in 250. The median tumor size was 7 cm. 144 tumors were localized, 131 regional and 178 distant (20 unknown). Median follow-up for 229 survivors was 8.17years. 5-year-DSS and OS was 49.7 % ± 4.9(95 % CI) and 46.3 % ± 4.9, respectively. A total of 169 patients underwent pathological examination of regional lymph nodes. In 51, one node was examined, in 24 two and in 63 ≥ 3 nodes were examined. Overall, 85 patients had pathologically positive nodes: 36 had one positive regional lymph node, 12 had two and 15 had ≥3. When adjusted for age, histology, size and stage, involvement of ≥3 lymph nodes was independently associated with worse survival. This observation was also applicable to the Cox regression analysis, which exclusively considered the 275 cases of localized/regional stage.
Conclusion: The number of regional lymph nodes affected correlates with survival, suggesting the extent of lymph node involvement as a new and crucial predictive factor. Further analysis of the extent of regional lymph node involvement is advisable. This includes identifying the most effective methods for detecting affected nodes and establishing how many nodes need to be examined to obtain representative results.

1. Introduction

Soft tissue sarcomas (STS) account for 1.5 % of cancers in adults [1]. At 7.4 %, they are more common in children [1]. Rhabdomyosarcoma (RMS) is the most common STS in childhood but also occurs in adulthood [1–23]. In childhood, approximately 15 % of RMS are located at extremities, while in adulthood, extremity RMS account for approximately 25 % [1,3,7,19,20,24–27]. Extremity site enables radical local therapies including mutilating surgery [4]. Nevertheless, it is associated with a poorer prognosis compared to other sites and classified as unfavorable [2,3,5–7,9,14,21,22,25,26,28–31]. In extant pediatric studies on extremity RMS, advanced age, alveolar subtypes, lymph node involvement and distant metastases have been identified as unfavorable factors. [3,4,7–9,24,26]. Both adult and pediatric literature report an association between lymph node involvement and poorer survival [3,4,7–9,24,26,27,32]. Consequently, the presence of regional lymph node involvement is a component of the international pediatric RMS risk stratification system [28,33,34]. In RMS, as well as in the broader group of STS, the presence of regional lymph node involvement has invariably been the subject of evaluations, irrespective of the number of affected nodes [3,4,6–9,24,26,32,35,36]. Therefore, the objective was to assess the impact of the precise number of pathologically examined and affected lymph nodes on long-term survival of extremity RMS using the population-based Surveillance, Epidemiology, and End Results (SEER) program.

* Corresponding author. Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Pediatric Hematology and Oncology, Augustenburger Platz 1, 13353, Berlin, Germany.
E-mail address: monika.scheer@uk-essen.de (M. Scheer).

https://doi.org/10.1016/j.ejso.2025.110535
Received 17 July 2025; Received in revised form 12 October 2025; Accepted 20 October 2025
Available online 25 October 2025

2. Methods

Data were obtained from the SEER 17 database (2000–2020). Inclusion criteria were: (1) malignant behavior, (2) known age, (3) histology ICD-O-3 8900/3, 8902/3, 8910/3, 8912/3, 8920/3, 8921/3, (4) positive histology, (5) first malignancy (sequence number: one primary only or 1st of 2 or more primaries), (6) tumor located in extremities C40.0, C40.2, C40.3, C44.7, C49.1, C49.2. Death certificate cases were excluded (Fig. 1). Ethical vote was obtained from the Charité Ethics Committee.

We classified selected cases in the categories: <10-year-olds, 10-17-year-olds, 18-39-year-olds, 40-64-year-olds and ≥65-year-olds. A second classification focused on adolescents and young adults (AYA): <15-year-olds, 15-39-year-olds (AYAs), 40-64-year-olds and ≥65-year-olds.

We categorized the number of pathologically examined and pathologically affected regional nodes as 1, 2 and ≥ 3. The extent of regional

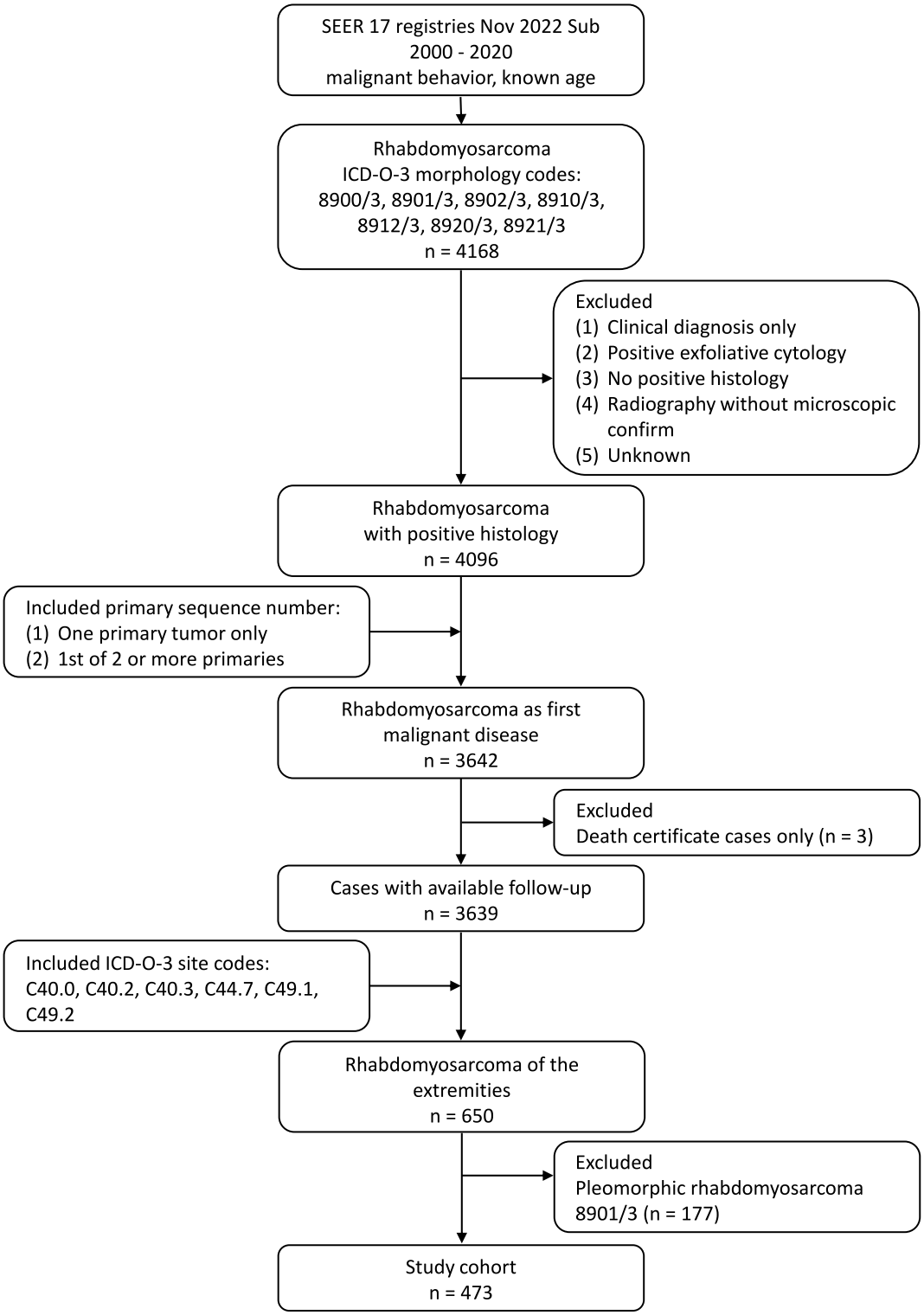

Fig. 1. Patient selection (CONSORT).

lymph node surgery was coded as 1, 2, ≥3, sentinel lymph node biopsy, aspiration of regional lymph nodes and number of regional lymph nodes removed unknown.

2.1. Statistical methods

We used the SEER*Stat software for patient selection. Statistics were calculated using IBM SPSS® 29 (Armonk, New York, U.S.). The Chi^2-test was used to compare distributions. Kaplan-Meier estimator was used to calculate overall survival (OS) and disease-specific survival (DSS) probabilities with 95 %-confidence intervals [37]. OS was defined as the time from diagnosis to death or last follow-up. DSS was defined as the time from diagnosis to death due to this disease. Patients alive/without event were censored at last follow-up. For comparison, the log-rank test was used. To identify independent predictive factors, potentially relevant factors were included in the Cox proportional hazards regression analysis. The resulting hazard ratios (HRs) with 95 %-confidence intervals were calculated using the Wald method.

To identify factors correlating with lymph node affection, a binary regression analysis was conducted, with pathological regional lymph node affection as the endpoint (patients of localized/regional stage).

3. Results

3.1. Characteristics

A total of 473 cases with non-pleomorphic extremity RMS met the inclusion criteria. 181 (38 %) tumors were located on upper, 292 (62 %) on lower limbs. Median age was 14years (range 0–90+). 153 (32 %) patients were <10-years, 135 (29 %) 10-17-years, 87 (18 %) 18-39-years, 69 (15 %) 40-64-years and 29 (6 %) ≥65-years (Fig. 2, Table 1). Overall, 213 (45 %) were females, 260 (55 %) males. The most common histologic subtypes were alveolar (ARMS) in 250 (53 %) and embryonal (ERMS) in 60 (13 %) with 110 (23 %) being RMS-NOS (Table 1). For those 394 with documented tumor size, median size was 7 cm. Overall, 144 (30 %) patients had localized, 131 (28 %) regional and 178 (38 %) distant tumor stage (20, 4 % unknown). Characteristics differed according to upper and lower limb and according to age group (Supplementary Table 1).

3.2. Regional lymph nodes – pathological examination and involvement

Overall, a total of 169 patients underwent pathological examination of regional lymph nodes. Regarding tumor site, regional lymph nodes were examined in 76/181 (42 %) patients with upper extremity and 93/292 (32 %) with lower extremity RMS. 41 upper and 44 lower extremity RMS exhibited pathological lymph node involvement (supplementary_Table 1a).

Regarding the number of pathologically examined lymph nodes, 1 lymph node was examined in 51 patients, 2 nodes in 24, ≥3 in 63 patients (Table 1). Overall, 85 patients exhibited affected regional lymph nodes. 36 had 1 positive node, 12 had 2, 15 had ≥3. In patients <18years 1 single node was most frequently examined or positive. With increasing age, lymph nodes were examined less frequently. Consequently, pathological lymph node involvement was less frequent (supplementary_Table 1b/c). Regarding the extent of regional lymph node surgery, sentinel techniques were performed in 40 (8 %) patients (Table 1).

In the subgroup of those 275 patients with localized/regional stage only, 126 lymph nodes were pathologically examined. 46 had pathologically affected regional lymph nodes, 73 unaffected nodes (7 result not documented).

Among the 178 distant stage patients, 39 had pathologically positive nodes. A total of five patients exhibited combined regional and distant lymph node involvement.

3.3. Outcome

For all patients, 3-, 5-, and 10-year overall survival (OS) rates were 57.2 % ± 4.7 (95 % confidence interval [CI]), 46.3 % ± 4.9, and 41.2 % ± 4.9, respectively. 3-, 5-, and 10-year disease-specific survival (DSS) rates were 59.8 % ± 4.7, 49.7 % ± 4.9, and 44.8 % ± 5.1, respectively (Fig. 2). With median follow-up of 8.17 years (range 0–20.92) for survivors, 229 (48 %) patients were alive at the cut-off date. Overall, 244 (52 %) patients died. 219 patients died of the disease.

For patients with localized/regional stage, 5-year OS and DSS was 62.4 % ± 6.1 and 66.5 % ± 6.1, respectively.

3.4. Factors for survival

In univariate analysis, factors associated with adverse DSS and OS were older age, male gender, SRMS and ARMS beside RMS-NOS histology, location at lower limb, increasing tumor size, distant tumor stage, no pathological examination of regional lymph nodes and pathological regional lymph node involvement (Table 1, Fig. 2, supplementary_Fig. 1).

Although pathological examination of lymph nodes was associated with better survival, no clear trend towards examining a larger number of nodes could be observed (Fig. 3). Survival was adverse for patients with pathologically affected lymph nodes. It deteriorated with an increasing number of pathologically affected lymph nodes.

Regarding the extent of regional lymph node surgery, patients with 2 regional lymph nodes examined showed best survival, followed by patients with sentinel lymph node biopsy. In contrast, adverse survival was observed with aspiration of regional lymph nodes.

3.5. Cox's proportional hazards regression analysis (number of pathologically examined and number of pathologically affected regional lymph nodes)

In order to ascertain the independent correlation between the number of regional lymph nodes examined and additionally the number of pathological positive nodes with OS and DSS, a Cox regression analysis was conducted for the entire cohort (all disease stages) and additionally for those patients with localized/regional disease only (adjusted for age, histology, tumor size, disease stage) (Table 2). ≥3 pathologically positive nodes were associated with adverse OS and DSS in patients of all disease stages and in those with localized/regional disease stage only (HR all stages 2.433; $p = 0.016$, HR loc/reg 4.769; $p = < 0.001$). In both groups, the number of nodes examined was not predictive. In addition, factors associated with adverse OS and DSS were older age, larger tumor size and higher disease stage.

3.6. Binary regression analysis for pathologically positive regional lymph nodes in localized/regional disease stage

To analyze the correlation between the extent of regional lymph node surgery and the detection of affected nodes, we conducted a binary regression analysis of patients with localized/regional stage and pathologically examined lymph nodes. Alveolar histology was associated with the highest probability for an affected node while the number of examined nodes and technique did not reach significance (Table 3).

Further information on the conducted therapy modalities and sites of metastasis can be found in the supplementary files.

4. Discussion

Extremity RMS are aggressive tumors, particularly prevalent in children, with high propensity for metastases [2,3,6,8,13,27,38]. This comprehensive, cross-sectional study of 473 cases revealed that not only regional lymph node affection, but moreover the number of pathologically affected regional lymph nodes, is predictive. Besides, patient age,

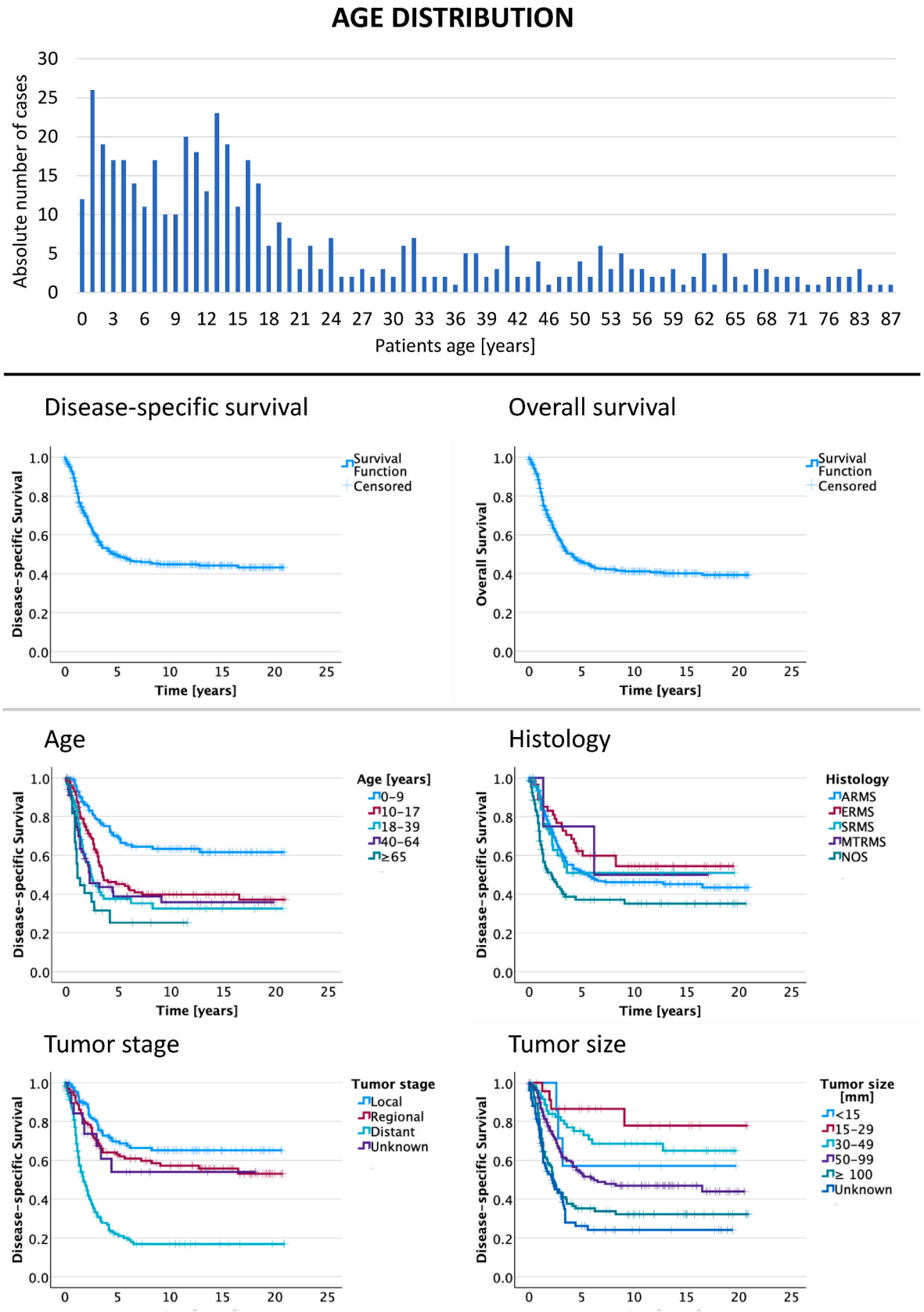

Fig. 2. Age distribution of the entire cohort. Overall and disease-specific survival probability for the whole cohort and disease-specific survival according to age groups, RMS histology, tumor size and stage.

Table 1
Univariate analysis of patient and tumor characteristics.

	n	%	5-year DSS (%)	95 % CI	*p-value*	5-year OS (%)	95 % CI	*p-value*
All patients								
Age [years]					***<0.001***			***<0.001***
<10	153	(32)	69.2	8.0		64.3	8.2	
10–17	135	(29)	45.2	9.2		42.7	9.0	
18–39	87	(18)	37.6	11.6		36.5	11.4	
40–64	69	(15)	38.8	12.9		34.3	12.2	
≥65	29	(6)	25.2	18.2		21.6	17.1	
Age [years]					***<0.001***			***<0.001***
<15	246	(52)	59.3	6.9		54.8	6.7	
15-39 (AYAs)	129	(27)	42.4	9.4		41.7	9.2	
40–64	69	(15)	38.8	12.9		34.3	12.2	
≥65	29	(6)	25.2	18.2		21.6	17.1	
Sex					***0.011***			***0.026***
Female	213	(45)	56.8	7.3		52.2	7.3	
Male	260	(55)	44.0	6.7		41.5	6.5	
Year of diagnosis					*0.319*			*0.341*
2000–2004	114	(24)	55.5	9.4		50.8	9.2	
2005–2009	119	(25)	52.2	9.2		49.9	9.0	
2010–2014	106	(22)	40.7	9,8		37.0	9.2	
2015–2020	134	(28)	50.6	12.0		48.1	11.8	
Primary site					*0.369*			*0.247*
C49.1	181	(38)	55.4	7.8		52.5	7.6	
C49.2	282	(60)	45.8	6.5		42.8	6.3	
C40.2	8	(2)	50.0	40.0		37.5	33.5	
C40.3	1	(<0.5)	0 %			0 %		
C44.7	1	(<0.5)	100 %[a]			0 %		
RMS Histology					***0.002***			***<0.001***
Alveolar	250	(53)	51.5	6.9		48.5	6.7	
Embryonal, NOS	60	(13)	62.3	13.5		59.1	13.5	
Spindle cell	49	(10)	51.0	16.1		45.4	15.7	
Mixed type	4	(<1)	75.0	42.5		75.0	42.5	
RMS, NOS	110	(23)	37.1	10.2		34.3	9.6	
Localization					*0.068*			***0.025***
Upper limb	181	(38)	55.4	7.8		52.5	7.6	
Lower limb	292	(62)	45.8	6.5		42.2	6.3	
Tumor size [mm]					***<0.001***			***<0.001***
<15	7	(1)	57.1	36.7		57.1	36.7	
15–29	24	(5)	86.5	14.1		82.0	16.1	
30–49	76	(16)	75.1	10.8		71.0	11.2	
50–99	170	(36)	53.3	8.4		50.7	8.2	
≥100	117	(25)	35.2	9.4		32.3	9.2	
Unknown	79	(17)	26.2	11.0		23.0	9.8	
Tumor stage					***<0.001***			***<0.001***
Localized	144	(30)	69.8	8.4		64.1	8.6	
Regional	131	(28)	63.1	8.8		60.6	8.8	
Distant	178	(38)	22.0	7.1		20.2	6.7	
Unknown	20	(4)	54.0	23.9		46.7	22.9	
Tumor stage in detail					***<0.001***			***<0.001***
Localized	144	(30)	69.8	8.4		64.1	8.6	
Regional								
- direct extension only	38	(8)	64.4	15.5		62.7	15.5	
- direct extension&lymph node involv.	13	(3)	25.0	24.5		23.1	22.9	
- lymph nodes involved only	36	(8)	56.2	16.9		56.2	16.9	
- not specified	44	(9)	84.6	11.4		78.7	13.3	
Distant	178	(38)	22.0	7.1		20.2	6.7	
Unknown	20	(4)	54.0	23.9		46.7	22.9	
RLN examination					***0.002***			***<0.001***
No	281	(59)	43.1	6.5		39.6	6.1	
Yes	169	(36)	61.3	8.0		58.1	8.0	
Unknown	23	(5)	40.0	26.3		38.2	25.3	
Interval from diagnosis to treatment [months]					***<0.001***			***<0.001***
0	254	(54)	56.2	6.7		52.2	6.5	
1	170	(36)	44.7	8.6		41.3	8.4	
2	20	(4)	20.3	19.8		19.3	19.0	
3	6	(1)	50.0	40.0		50.0	40.0	
4	5	(1)	75.0	42.5		75.0	42.5	
Unavailable	18	(4)	26.7	21.0		26.7	21.0	

(*continued on next page*)

Table 1 (*continued*)

	n	%	5-year DSS (%)	95 % CI	*p-value*	5-year OS (%)	95 % CI	*p-value*
Number of RLNs examined					***<0.001***			***<0.001***
0	281	(59)	43.1	6.5		39.6	6.1	
1	51	(11)	59.1	15.5		55.2	15.5	
2	24	(5)	81.0	16.9		77.6	17.4	
≥3	63	(13)	67.8	12.3		66.6	12.3	
Aspiration of RLNs	15	(3)	22.1	26.1		22.1	26.1	
Number of RLNs removed unknown	16	(3)	41.9	26.5		33.5	23.9	
Unknown	23	(5)	40.0	26.3		38.2	25.3	
RLN involvement					***<0.001***			***<0.001***
N0	84	(18)	77.9	10.0		74.3	10.4	
N1	85	(18)	45.6	11.6		42.8	11.4	
NX	23	(5)	40.0	26.3		38.2	24.9	
No RLNs examined	281	(59)	43.1	6.5		39.6	6.1	
Number of positive RLNs					***<0.001***			***<0.001***
0	84	(18)	77.9	10.0		74.3	10.4	
1	36	(8)	54.5	17.2		54.5	17.2	
2	12	(3)	72.7	26.3		66.7	26.7	
≥3	15	(3)	22.2	22.0		22.2	22.0	
RLNs positive, number unknown	22	(5)	29.1	22.9		17.8	20.4	
No RLNs examined	281	(59)	43.1	6.5		39.6	6.1	
Unknown	23	(5)	40.0	26.3		38.2	25.3	
Extent of RLN surgery including sentinel biopsy and aspiration					***0.003***			***0.002***
0	281	(59)	43.1	6.5		39.6	6.1	
1	38	(8)	56.0	17.8		56.0	17.8	
2	16	(3)	80.0	20.2		75.0	21.2	
≥3	48	(10)	61.7	14.9		60.1	14.9	
Sentinel LN biopsy	40	(8)	72.7	15.3		67.7	15.9	
Aspiration of RLNs	14	(3)	24.0	28.0		24.0	28.0	
Number of RLNs removed unkn.	14	(3)	49.0	29.0		38.7	26.5	
Unknown	22	(5)	39.9	26.3		38.0	25.3	
Subgroup analysis of localized & regional stage only (275 cases)								
localized & regional – Regional lymph node examination					*0.126*			*0.079*
No	149	(54)	61.5	8.4		57.4	8.4	
Yes	119	(43)	73.1	8.8		69.0	9.0	
Unknown	7	(3)	60.0	42.9		60.0	42.9	
localized & regional – Number of regional lymph nodes examined					*0.386*			*0.215*
0	149	(54)	61.5	8.4		57.4	8.4	
1	34	(12)	71.4	18.8		64.9	19.2	
2	18	(7)	82.6	17.8		82.6	17.8	
≥3	50	(18)	75.4	12.7		73.8	12.7	
Aspiration of RLNs	5	(2)	60.0	42.9		60.0	42.9	
Number of RLNs removed unkn.	12	(4)	58.3	31.6		45.5	29.4	
Unknown	7	(3)	60.0	42.9		60.0	42.9	
localized & regional – Regional lymph node involvement					***0.035***			***0.029***
N0	73	(27)	82.6	9.8		78.4	10.6	
N1	46	(17)	59.2	15.1		55.2	15.3	
NX	7	(3)	60.0	42.9		60.0	42.9	
No RLNs examined	149	(54)	61.5	8.4		57.4	8.4	
localized & regional – Number of positive regional lymph nodes					***0.006***			***0.007***
0	73	(27)	82.6	9.8		78.4	10.6	
1	20	(7)	65.8	22.7		65.8	22.7	
2	10	(4)	70.0	28.4		70.0	28.4	
≥3	8	(3)	25.0	30.0		25.0	30.0	
RLNs positive, number unknown	8	(3)	71.4	33.5		40.0	39.8	
No RLNs examined	149	(54)	61.5	8.4		57.4	8.4	
Unknown	7	(3)	60.0	42.9		60.0	42.9	
localized & regional – Sequencing of radiation and surgery					*0.111*			***0.028***
Radiation before surgery	17	(6)	65.5	24.7		65.5	24.7	
Radiation after surgery	124	(45)	74.8	8.0		72.5	8.2	
Radiation before and after surgery	2	(<1)	100 %			50.0	69.4	
Intraoperative radiation	1	(<0.5)	100 %			100 %		
Intraoperative radiation with other radiation given before and/or after surgery	5	(2)	66.7	53.3		66.7	53.3	
Surgery before and after radiation	1	(<0.5)	100 %[b]			100 %[b]		
No radiation and/or surgery	125	(45)	56.4	9.8		50.7	9.6	

Variables with a p-value less than 0.05 in the univariate analysis were considered statistically significant.
C49.1-Connective, subcutaneous, other soft tissue: upper limb, shoulder.
C49.2-Connective, subcutaneous, other soft tissue: lower limb, hip.
C40.2-Long bones of lower limb and associated joints.
C40.3-Short bones of lower limb and associated joints.
C44.7-Skin of lower limb and hip.
[a] Last follow up: 3.00 years.
[b] Last follow-up: 1.67 years.

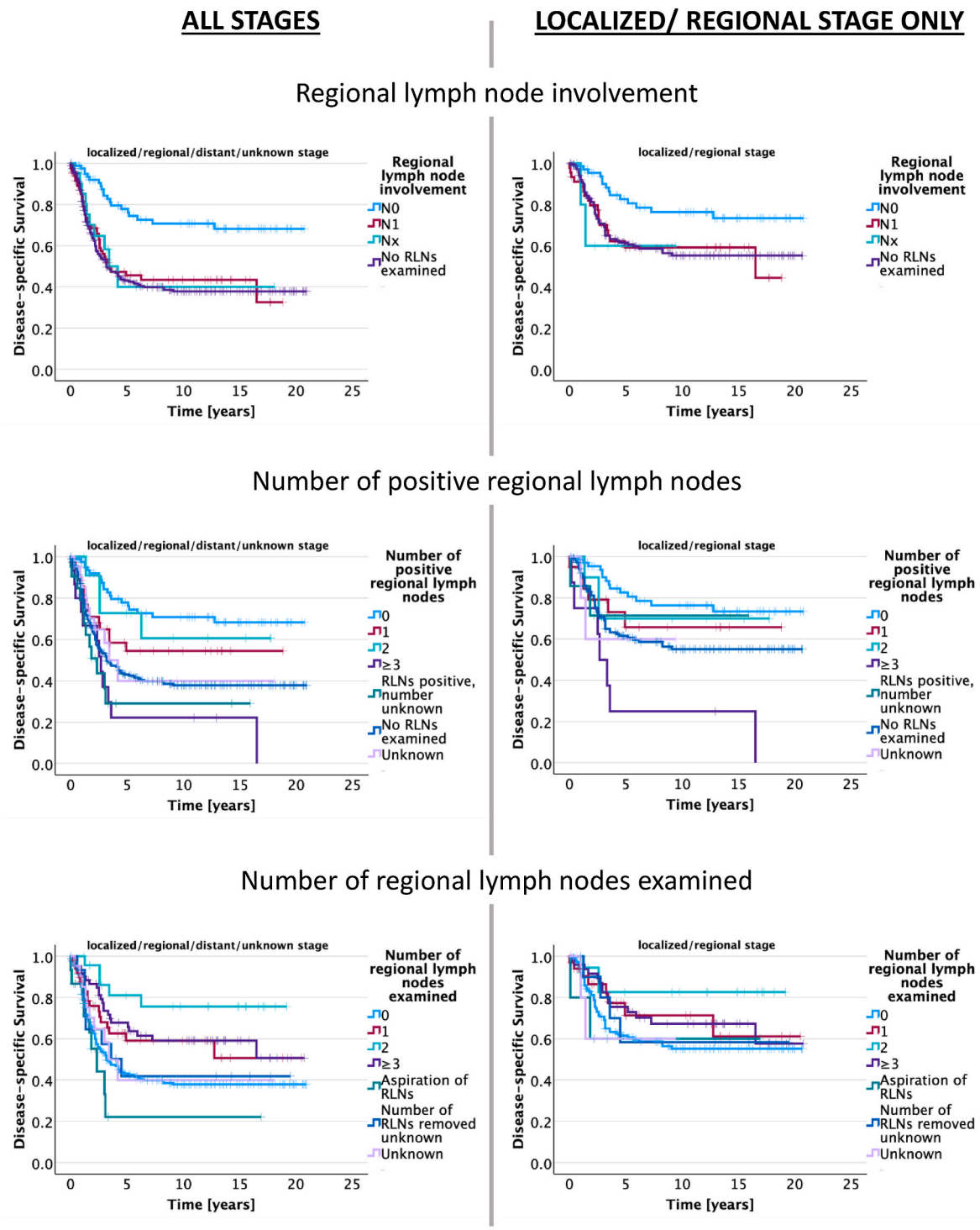

Fig. 3. Disease-specific survival according to regional lymph node involvement, exact number of pathologically positive regional lymph nodes and exact number of regional lymph nodes examined for all stages and localized/regional stage only.

tumor size, tumor stage are independent predictive factors.

In this cross-age cohort, 5-year OS and DSS were 46.3 % ± 4.9 and 49.7 % ± 4.9, respectively. Among patients with localized/regional disease, rates improved to 62.4 % ± 6.1 and 66.5 % ± 6.1. In literature, 5-year OS is reported between 55 % and 59 % for pediatric extremity RMS of all stages [3,8,28]. Reported 5-year OS for pediatric localized stage was 67 %–84 % [3,7,24,26,39]. The median age of this cohort was 14 years. Consistent with prior findings, the majority of patients were male (55 %) [1,3,7,8,24,26], with tumors predominantly in the lower extremities [3,7–9,24,26]. ARMS was the most common subtype [3,4,7–10,24,40] and the median tumor size was 7 cm —larger than typically reported in pediatric RMS across all sites [40] while this corresponds to the pediatric study of extremity RMS by Oberlin, where most tumors were >5 cm^2 [6]. Disease stages were evenly distributed, resulting in high rates of regional and distant spread.

Of 473 patients, 169 underwent pathological evaluation of regional lymph nodes. Among the 275 patients with localized/regional disease, 126 had lymph nodes examined. Most had at least three nodes assessed, with one node being the second most common. Pathological nodal involvement was found in 85 of the 169 examined patients, including 46

Table 2
Cox Regression analysis including age, histology, tumor size, tumor stage, exact number of pathologically positive regional lymph nodes (first model), exact number of regional lymph nodes examined (second model) for localized/regional stage only and all stages.

	Disease-specific Survival				Overall Survival			
	Hazard Ratio	95 % CI Lower	95 % CI Upper	*p-value*	Hazard Ratio	95 % CI Lower	95 % CI Upper	*p-value*
first model – patients with localized and regional stage only								
Age continuously [years]	1.021	1.009	1.032	***<0.001***	1.021	1.011	1.032	***<0.001***
Histology								
Non-ARMS	1				1			
ARMS	1.091	0.642	1.853	*0.747*	1.018	0.622	1.668	*0.942*
Tumor size								
<50 mm	1				1			
≥50 mm	3.256	1.696	6.249	***<0.001***	2.935	1.641	5.252	***<0.001***
Unknown	4.729	2.029	11.021	***<0.001***	4.138	1.895	9.034	***<0.001***
Number of positive RLNs								
0	1				1			
1	1.381	0.524	3.637	*0.513*	1.187	0.463	3.045	*0.721*
2	1.776	0.503	6.277	*0.372*	1.493	0.432	5.163	*0.527*
≥3	4.769	1.882	12.084	***<0.001***	4.135	1.678	10.190	***0.002***
RLNs positive, number unknown	1.689	0.377	7.567	*0.493*	2.626	0.863	7.991	*0.089*
No RLNs examined	1.237	0.654	2.339	*0.513*	1.183	0.661	2.119	*0.572*
Unknown	1.175	0.246	5.607	*0.840*	0.955	0.205	4.451	*0.953*
second model – patients with localized and regional stage only								
Age continuously [years]	1.020	1.009	1.032	***<0.001***	1.021	1.010	1.032	***<0.001***
Histology								
Non-ARMS	1				1			
ARMS	1.120	0.661	1.898	*0.673*	1.032	0.632	1.687	*0.900*
Tumor size								
<50 mm	1				1			
≥50 mm	3.497	1.832	6.675	***<0.001***	3.116	1.749	5.551	***<0.001***
Unknown	4.757	2.029	11.153	***<0.001***	4.084	1.861	8.964	***<0.001***
Number of RLNs examined								
0	1				1			
1	1.038	0.466	2.312	*0.927*	1.172	0.569	2.416	*0.667*
2	0.735	0.222	2.429	*0.613*	0.624	0.190	2.046	*0.436*
≥3	1.138	0.608	2.129	*0.687*	1.062	0.583	1.933	*0.835*
Aspiration of RLNs	2.513	0.587	10.760	*0.214*	2.256	0.530	9.596	*0.271*
Number of RLNs removed unkn.	1.450	0.494	4.241	*0.497*	1.852	0.753	4.557	*0.179*
Unknown	0.983	0.230	4.196	*0.981*	0.837	0.197	3.550	*0.809*
first model – patients of all disease stages								
Age continuously [years]	1.026	1.018	1.035	***<0.001***	1.026	1.018	1.033	***<0.001***
Histology								
Non-ARMS	1				1			
ARMS	1.027	0.739	1.427	*0.876*	0.979	0.716	1.338	*0.894*
Tumor size								
<50 mm	1				1			
≥50 mm	1.889	1.242	2.871	***0.003***	1.807	1.226	2.663	***0.003***
Unknown	3.041	1.847	5.004	***<0.001***	2.918	1.834	4.641	***<0.001***
Tumor stage								
Localized	1				1			
Regional	1.977	1.268	3.083	***0.003***	1.664	1.104	2.508	***0.015***
Distant	5.943	3.937	8.971	***<0.001***	4.937	3.389	7.191	***<0.001***
Unknown	1.298	0.574	2.934	*0.531*	1.376	0.677	2.799	*0.378*
Number of positive RLNs								
0	1				1			
1	1.044	0.528	2.064	*0.902*	0.974	0.502	1.891	*0.939*
2	1.179	0.398	3.497	*0.766*	1.359	0.509	3.628	*0.540*
≥3	2.433	1.176	5.031	***0.016***	2.273	1.119	4.619	***0.023***
RLNs positive, number unknown	2.209	1.056	4.623	***0.035***	2.365	1.190	4.701	***0.014***
No RLNs examined	1.429	0.875	2.334	*0.153*	1.405	0.887	2.224	*0.147*
Unknown	0.909	0.401	2.062	*0.820*	0.938	0.440	2.002	*0.869*
second model– patients of all disease stages								
Age continuously [years]	1.026	1.018	1.035	***<0.001***	1.025	1.018	1.033	***<0.001***
Histology								
Non-ARMS	1				1			
ARMS	0.990	0.708	1.383	*0.952*	0.948	0.690	1.303	*0.774*
Tumor size								
<50 mm	1				1			

(*continued on next page*)

Table 2 (*continued*)

	Disease-specific Survival				Overall Survival			
	Hazard Ratio	95 % CI Lower	95 % CI Upper	*p-value*	Hazard Ratio	95 % CI Lower	95 % CI Upper	*p-value*
≥50 mm	1.955	1.286	2.972	***0.002***	1.847	1.254	2.720	***0.002***
Unknown	3.100	1.884	5.102	***<0.001***	2.974	1.869	4.731	***<0.001***
Tumor stage								
Localized	1				1			
Regional	1.977	1.272	3.073	***0.002***	1.665	1.108	2.502	***0.014***
Distant	6.270	4.181	9.403	***<0.001***	5.215	3.604	7.547	***<0.001***
Unknown	1.361	0.602	3.076	*0.459*	1.435	0.706	2.916	*0.319*
Number of RLNs examined								
0	1				1			
1	0.819	0.493	1.361	*0.441*	0.859	0.530	1.391	*0.536*
2	0.487	0.195	1.214	*0.123*	0.521	0.226	1.201	*0.126*
≥3	0.891	0.560	1.417	*0.625*	0.850	0.541	1.336	*0.481*
Aspiration of RLNs	1.541	0.771	3.082	*0.221*	1.459	0.732	2.906	*0.283*
Number of RLNs removed unkn.	1.768	0.841	3.718	*0.133*	1.964	1.003	3.845	***0.049***
Unknown	0.631	0.321	1.239	*0.181*	0.659	0.355	1.224	*0.187*

RLN = Regional lymph node.

Table 3
Binary regression analysis with the endpoint of a pathologically affected regional lymph node - including extent of regional lymph nodes surgery, age, tumor size and histology for patients with localized/regional stage only and examined regional lymph nodes.

	Regional lymph node involvement			
	Odds Ratio	95 % CI Lower	95 % CI Upper	*p-value*
Extent of RLN surgery				
≥3	1			
1	1.336	0.439	4.067	*0.610*
2	0.572	0.119	2.739	*0.484*
Sentinel LN biopsy	0.417	0.129	1.347	*0.144*
Aspiration of RLNs	2.991	0.283	31.654	*0.363*
Number of RLNs removed unkn.	0.987	0.240	4.065	*0.985*
Age continuously [years]	1.023	0.992	1.055	*0.149*
Tumor size continuously [mm]	1.001	0.999	1.003	*0.433*
Histology				
Non-ARMS	1			
ARMS	4.868	1.725	13.733	***0.003***

Among those 126 patients with localized/regional disease stage and pathological examination of regional lymph nodes, 46 exhibited affected lymph nodes, while 73 had no evidence of tumor cells in the examined lymph node (7 result of pathological examination unknown). These 7 patients with NX status were consequently excluded from binary regression analysis. Thus, a total of 119 patients with pathological lymph node examination were included in the analysis.

of the 126 with localized/regional disease. In most cases, only one positive node was identified.

Regional lymph node involvement is a well-established risk factor in international RMS-risk-stratification-systems [28,33,34]. Both pediatric and adult literature report its association with reduced overall survival [3,4,7–9,24,26,27,32]. In pediatric extremity RMS, regional nodal disease occurs in ~40 % and is particularly prognostic in ARMS [41–43]. Nevertheless, the prognostic impact is typically assessed without considering the number of involved nodes [3,4,6–9,24,26,32,35,36], despite growing evidence from other malignancies that nodal count may hold prognostic value [44–49]. Initial investigation of regional lymph nodes includes clinical examinations, sonography, MRI, FDG-PET-scan and/or biopsy of suspicious nodes [3,7,24,26,27,36,50,51]. Pediatric guidelines recommend surgical lymph node staging in all extremity RMS [43] regardless of imaging results [7,24,27,50,52,53], as imaging alone misses up to 20 % of nodal involvement [7,24,51]. The optimal number of regional lymph nodes to sample is not yet established (except in paratesticular RMS >10 years) [43,54].

To elucidate whether the extent of regional lymph node involvement is prognostic, we analyzed both the number of nodes examined and those affected. While we hypothesized that examining more nodes would improve detection and reduce false negatives, no survival benefit was observed for ≥3 nodes examined. In contrast, lymph node aspiration was associated with poorer outcomes. When adjusted for age, histology, stage, and size, the number of examined lymph nodes demonstrated no correlation with outcomes either. However, survival worsened with increasing numbers of affected nodes in univariate analysis. In multivariate analysis, involvement of ≥3 lymph nodes was independently associated with poorer survival—both in patients with localized/regional disease and across all stages, including metastatic disease. This finding must be interpreted cautiously, as the number of positive nodes depends on the number of nodes examined.

In patients with localized/regional disease and pathological node evaluation, binary regression revealed alveolar histology as the strongest predictor of nodal involvement. Neither the number of nodes examined nor techniques such as aspiration or sentinel node biopsy showed significance for nodal involvement, likely due to limited case numbers.

Regional nodal involvement influences risk stratification, including the intensity of systemic therapy and radiation fields [52,53]. Affected lymph nodes require local therapy, usually radiotherapy [3,4,7,8,19,27,50]. Treatment of the entire lymph node station is recommended, if only one node is affected [24,51]. Future studies should define optimal techniques and thresholds for nodal evaluation to guide risk stratification and treatment planning. Importantly, we assume that the extent of lymph node spread might be more critical than currently expected, even regardless of the existence of hematogenous spread distant metastases. For those with both distant metastases and regional lymph node involvement, this results in very poor outcomes. This aggressive subgroup should be prioritized in research. Nevertheless, a selection of cases who underwent pathological lymph node examination cannot be excluded. Furthermore, the decision regarding the selection of lymph nodes to be removed, as well as the number to be extracted, is contingent upon the surgeon's expertise and experience. As such, the criteria leading to pathological node evaluation may bias outcomes.

Comprehensive age-spanning data on extremity RMS, from childhood to older adulthood, are limited, which hinders the planning of investigations that span multiple age groups. In this cohort, increasing age was independently correlated with adverse survival. This is consistent with results for all RMS sites [1,32]. According to pediatric RMS protocols, patients are categorized in <1year, 1–9years and ≥10years [2,5,6,8,11,39], while ≥10years is considered unfavorable in terms of

risk stratification [30,33,34,39,55]. To enable cross-age comparisons relevant for clinical trial design, two age classifications were implemented. These were informed by the 18-year age limit that differentiates between pediatric and adult populations, as well as the incorporation of the AYA (Adolescents and Young Adults) age classification. AYA (15-39-year-olds) has only recently been defined, following the recognition that AYA patients exhibit distinct differences in terms of cancer types, risk factors, tumour biology, and prognosis [56,57]. In this series, 5-year survival of AYAs was better than that of 40-64-year-olds. Müller et al. showed poorer survival for patients aged 15–29years than >60years [58].

Characteristics differed according to age group. ARMS occurred frequently in <10-year- and 10-17-year-olds, while non-ARMS (especially NOS-RMS) increased from 18years onwards. Tumor size increased with patients' age. Disease was predominantly localized in 40-64-year- and ≥65-year-olds, whereas distant stage was most common in 10-17-year- and 18-39-year-olds. When evaluating therapy data, surgery was applied more frequently in older age groups, while chemotherapy and radiotherapy were more common in younger patients.

Previous analyses of our group demonstrated significant prognostic differences for granular subsites within the RMS sites of head/neck and the so-called other site [59,60]. Therefore, an investigation was conducted into the characteristics of upper and lower extremity. Histology and size differed significantly. RMS of upper limbs were more often ARMS and small. Pathologic examination of lymph nodes as well as involvement was more frequent in the upper extremity. Lower extremity RMS exhibited adverse survival in comparison to upper limbs. Oberlin et al. subdivided into distal and proximal extremity with tendential poorer prognosis for distal RMS [26]. In this cohort, tumor sizes >100 mm were associated with poorer survival, consistent with other cross-age STS studies [35,58,61]. Pediatric extremity RMS studies showed significantly poorer survival for >5 cm [4,8,26]. A shorter interval between diagnosis and treatment was favorable.

Given the propensity of extremity RMS to metastasize, a comprehensive analysis was conducted to ascertain the site and number of affected organs. Overall, 178 (38 %) patients had distant stages. Bone metastases were most common, followed by lungs. Patients with isolated lung metastases had worse 5-year survival compared to isolated bone. Consistent with literature, multiple metastatic sites correlated with poor survival [2,5,6,11,13,38]. In a pediatric study on extremity RMS, de Traux de Wardin et al. reported bone and bone marrow as the most frequent metastatic sites [3]. Pediatric series show that bone metastases are linked to poorer survival than lung metastases [5,6,11]. Bone and bone marrow involvement are often analyzed together [6,38]. A key limitation is that SEER does not record bone marrow infiltration as a separate variable.

The large number of patients over the lifespan from a population-based epidemiological registry is considered an outstanding strength of this evaluation. Given the relative frequency of RMS in children, most RMS trials were conducted with the inclusion of children/adolescents only [30,55], while recent COG trials also included adults [39,62,63]. To facilitate future cross-age trial designs a detailed description of characteristics within different age categorizations was presented.

The fact that the extent of regional lymph node involvement is critical underscores the importance of deeper research. At the same time, it emphasizes the importance of a standardized approach to lymph node staging. In real-world scenarios, it is often less standardized and optimized than intended and not always carried out as recommended [64,65]. The clinical implications of this novel result remain to be established and warrant further investigation. While a higher number of positive regional lymph nodes is associated with poorer survival, it remains to be elucidated how this should inform management in the future. Should clinical guidelines advocate for more aggressive local therapy, or should involvement of several regional lymph nodes be considered and stratified as distant metastases?

As with other retrospective, population-based studies, this analysis has major limitations that complicate the interpretation of the results. A key issue is the inherent selection bias, as the decision to perform lymph node evaluation is not random. Crucial information is lacking regarding the preoperative assessment of regional lymph nodes and the criteria guiding lymph node dissection. Details on the surgical techniques used are limited, and coding heterogeneity may further bias the findings. While the data reflect real-world clinical practice, variability in clinical decision-making has the potential to undermine the validity of the results. Additionally, the absence of imaging data in the SEER database represents a significant limitation, particularly regarding lymph node evaluation. Lymph node involvement may have been based on imaging, contributing to classification as SEER regional stage. To account for this, SEER stage (local, regional, distant) was included as recorded in the multivariable models. Additional limitations include the lack of data on central pathological review (major limitation in sarcoma research) and molecular markers, such as RMS fusion status [12,15,16,23,64,66]. Treatment details, including surgical extent, are also limited and must be interpreted with caution. In this regard, a major limitation of this study is the lack of data on reconstructive and functional outcomes. As a result, the critical balance between oncologic radicality and functional preservation—particularly relevant in regional lymph node surgery and essential for clinical translation—cannot be adequately assessed. Given the potential risks such as lymphedema and impaired recovery, future prospective studies should integrate functional outcome measures to support evidence-based, patient-centered surgical decision-making.

Nonetheless, the study offers important insights. In summary, after adjustment for other risk factors, the number of affected regional lymph nodes was independently associated with survival in both localized/regional disease and in patients across all stages, including those with metastatic disease. The extent of lymph node involvement might be a crucial and hitherto overlooked prognostic factor. Consequently, future studies should pay more careful attention to the extent of regional lymph node involvement. This includes identifying the most effective methods for detecting affected nodes and defining the number of nodes to be examined to achieve representative results. While the results presented herein require further validation through prospective, standardized investigations, we suggest that the number of affected regional lymph nodes be considered when refining RMS risk stratification.

Ethics statement

Ethical approval was obtained from the Charité ethics committee.

Data availability statement

The data are available at https://seer.cancer.gov/

Disclosure

None of the authors declares a conflict of interest related to the content of the manuscript.

Acknowledgments of research support

No funding support

Author credit

Luna Margotte: Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Project administration, Anton Henssen: Writing - Review & Editing, Anne Thorwarth: Writing - Review & Editing, Angelika Eggert: Writing - Review & Editing, Supervision, Monika Scheer: Conceptualization, Methodology, Validation, Investigation, Data Curation, Resources, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration.

Declaration of competing interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.110535.

References

[1] Ferrari A, Sultan I, Huang TT, et al. Soft tissue sarcoma across the age spectrum: a population-based study from the surveillance epidemiology and end results database. Pediatr Blood Cancer 2011;57(6):943–9.
[2] Schloemer NJ, Xue W, Qumseya A, et al. Prognosis of children and young adults with newly diagnosed rhabdomyosarcoma metastatic to bone marrow treated on children's oncology group studies. Pediatr Blood Cancer 2023;70(12):e30701.
[3] de Traux de Wardin H, Xu B, Dermawan JK, et al. Extremity Rhabdomyosarcoma-An integrated clinicopathologic and genomic study to improve risk stratification. JCO Precis Oncol 2023;7(1):e2200705.
[4] Lawrence Jr W, Hays DM, Heyn R, Beltangady M, Maurer HM. Surgical lessons from the Intergroup Rhabdomyosarcoma Study (IRS) pertaining to extremity tumors. World J Surg 1988;12(5):676–84.
[5] Carli M, Colombatti R, Oberlin O, et al. European intergroup studies (MMT4-89 and MMT4-91) on childhood metastatic rhabdomyosarcoma: final results and analysis of prognostic factors. J Clin Oncol 2004;22(23):4787–94.
[6] Oberlin O, Rey A, Lyden E, et al. Prognostic factors in metastatic rhabdomyosarcomas: results of a pooled analysis from United States and European cooperative groups. J Clin Oncol 2008;26(14):2384–9.
[7] Welmant J, Helfre S, Carton M, et al. Pattern of relapse in pediatric localized extremity rhabdomyosarcomas correlated with locoregional therapies administered. Strahlenther Onkol 2021;197(8):690–9.
[8] Zhu L, Sun Y, Wang X, et al. Survival stratification in childhood rhabdomyosarcoma of the extremities: a derivation and validation study. Sci Rep 2020;10(1):5684.
[9] Mandell L, Ghavimi F, LaQuaglia M, Exelby P. Prognostic significance of regional lymph node involvement in childhood extremity rhabdomyosarcoma. Med Pediatr Oncol 1990;18(6):466–71.
[10] Dagher R, Helman L. Rhabdomyosarcoma: an overview. Oncologist 1999;4(1):34–44.
[11] Vasquez JC, Luo LY, Hiniker SM, et al. Rhabdomyosarcoma with isolated lung metastases: a report from the soft tissue sarcoma committee of the Children's oncology group. Pediatr Blood Cancer 2023;70(6):e30293.
[12] Missiaglia E, Williamson D, Chisholm J, et al. PAX3/FOXO1 fusion gene status is the key prognostic molecular marker in rhabdomyosarcoma and significantly improves current risk stratification. J Clin Oncol 2012;30(14):1670–7.
[13] Breneman JC, Lyden E, Pappo AS, et al. Prognostic factors and clinical outcomes in children and adolescents with metastatic rhabdomyosarcoma–a report from the intergroup rhabdomyosarcoma study IV. J Clin Oncol 2003;21(1):78–84.
[14] Crist W, Gehan EA, Ragab AH, et al. The third intergroup rhabdomyosarcoma study. J Clin Oncol 1995;13(3):610–30.
[15] Yechieli RL, Mandeville HC, Hiniker SM, et al. Rhabdomyosarcoma. Pediatr Blood Cancer 2021;68(Suppl 2):e28254.
[16] Skapek SX, Anderson J, Barr FG, et al. PAX-FOXO1 fusion status drives unfavorable outcome for children with rhabdomyosarcoma: a children's oncology group report. Pediatr Blood Cancer 2013;60(9):1411–7.
[17] Miller RW, Young Jr JL, Novakovic B. Childhood cancer. Cancer 1995;75(1 Suppl):395–405.
[18] Ognjanovic S, Linabery AM, Charbonneau B, Ross JA. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975-2005. Cancer 2009;115(18):4218–26.
[19] Meza JL, Anderson J, Pappo AS, Meyer WH. Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on intergroup rhabdomyosarcoma studies III and IV: the children's oncology group. J Clin Oncol 2006;24(24):3844–51.
[20] Weiss AR, Lyden ER, Anderson JR, et al. Histologic and clinical characteristics can guide staging evaluations for children and adolescents with rhabdomyosarcoma: a report from the children's oncology group soft tissue sarcoma committee. J Clin Oncol 2013;31(26):3226–32.
[21] Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. J Clin Oncol 2001;19(12):3091–102.
[22] Stevens MC, Rey A, Bouvet N, et al. Treatment of nonmetastatic rhabdomyosarcoma in childhood and adolescence: third study of the international society of paediatric Oncology–SIOP malignant mesenchymal tumor 89. J Clin Oncol 2005;23(12):2618–28.
[23] Dehner CA, Rudzinski ER, Davis JL. Rhabdomyosarcoma: updates on classification and the necessity of molecular testing beyond immunohistochemistry. Hum Pathol 2024;147:72–81.
[24] Terwisscha van Scheltinga SEJ, Wijnen M, Martelli H, et al. Local staging and treatment in extremity rhabdomyosarcoma. A report from the EpSSG-RMS2005 study. Cancer Med 2020;9(20):7580–9.
[25] Oberlin O, Rey A, Sanchez de Toledo J, et al. Randomized comparison of intensified six-drug versus standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other chemotherapy-sensitive childhood soft tissue sarcomas: long-term results from the international society of pediatric oncology MMT95 study. J Clin Oncol 2012;30(20):2457–65.
[26] Oberlin O, Rey A, Brown KL, et al. Prognostic factors for outcome in localized extremity rhabdomyosarcoma. Pooled analysis from four international cooperative groups. Pediatr Blood Cancer 2015;62(12):2125–31.
[27] Morris CD, Tunn PU, Rodeberg DA, et al. Surgical management of extremity rhabdomyosarcoma: a consensus opinion from the Children's oncology group, the european pediatric soft-tissue sarcoma study group, and the cooperative weichteilsarkom studiengruppe. Pediatr Blood Cancer 2023;70(3):e28608.
[28] Maurer HM, Beltangady M, Gehan EA, et al. The intergroup rhabdomyosarcoma Study-I. A final report. Cancer 1988;61(2):209–20.
[29] Bisogno G, Pastore G, Perilongo G, et al. Long-term results in childhood rhabdomyosarcoma: a report from the Italian cooperative study RMS 79. Pediatr Blood Cancer 2012;58(6):872–6.
[30] Dantonello TM, Int-Veen C, Harms D, et al. Cooperative trial CWS-91 for localized soft tissue sarcoma in children, adolescents, and young adults. J Clin Oncol 2009;27(9):1446–55.
[31] Hays DM, Soule EH, Lawrence Jr W, et al. Extremity lesions in the intergroup rhabdomyosarcoma study (IRS-I): a preliminary report. Cancer 1982;49(1):1–8.
[32] Glumac S, Davidovic R, Dozic B, et al. Immunohistochemical expression of cyclin-dependent kinase inhibitors p16 and p57 in rhabdomyosarcoma. Pathol Res Pract 2021;225:153558.
[33] Haduong JH, Heske CM, Allen-Rhoades W, et al. An update on rhabdomyosarcoma risk stratification and the rationale for current and future children's oncology group clinical trials. Pediatr Blood Cancer 2022;69(4):e29511.
[34] Hibbitts E, Chi YY, Hawkins DS, et al. Refinement of risk stratification for childhood rhabdomyosarcoma using FOXO1 fusion status in addition to established clinical outcome predictors: a report from the children's oncology group. Cancer Med 2019;8(14):6437–48.
[35] Gusho CA, Fice MP, O'Donoghue CM, Gitelis S, Blank AT. A population-based analysis of lymph node metastasis in extremity soft tissue sarcoma: an update. J Surg Res 2021;262:121–9.
[36] Maduekwe UN, Herb JN, Esther RJ, Kim HJ, Spanheimer PM. Pathologic nodal staging for clinically node negative soft tissue sarcoma of the extremities. J Surg Oncol 2021;123(8):1792–800.
[37] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53(282):457–81.
[38] Koscielniak E, Rodary C, Flamant F, et al. Metastatic rhabdomyosarcoma and histologically similar tumors in childhood: a retrospective European multi-center analysis. Med Pediatr Oncol 1992;20(3):209–14.
[39] Oberoi S, Xue W, Qumseya A, et al. Extremity rhabdomyosarcoma in children, adolescents and young adults: a report from children's oncology group trials. Cancer 2025;131(12):e35929.
[40] Newton Jr WA, Soule EH, Hamoudi AB, et al. Histopathology of childhood sarcomas, intergroup rhabdomyosarcoma studies I and II: clinicopathologic correlation. J Clin Oncol 1988;6(1):67–75.
[41] Gallego S, Chi YY, De Salvo GL, et al. Alveolar rhabdomyosarcoma with regional nodal involvement: results of a combined analysis from two cooperative groups. Pediatr Blood Cancer 2021;68(3):e28832.
[42] Rodeberg DA, Garcia-Henriquez N, Lyden ER, et al. Prognostic significance and tumor biology of regional lymph node disease in patients with rhabdomyosarcoma: a report from the children's oncology group. J Clin Oncol 2011;29(10):1304–11.
[43] Terwisscha van Scheltinga S, Schoot RA, Routh JC, et al. Lymph node staging and treatment in pediatric patients with soft tissue sarcomas: a consensus opinion from the children's oncology group, European paediatric soft tissue sarcoma study group, and the cooperative weichteilsarkom studiengruppe. Pediatr Blood Cancer 2025;72(4):e31538.
[44] Jakub JW, Russell G, Tillman CL, Lariscy C. Colon cancer and low lymph node count: who is to blame? Arch Surg 2009;144(12):1115–20.
[45] Wei B, Tan HL, Chen L, Chang S, Wang WL. How many lymph nodes are enough in thyroidectomy? A cohort study based on real-world data. Ann Surg Oncol 2025;32(2):1149–57.
[46] Sachs TE. Too many or too few? How many lymph nodes are enough? Ann Surg Oncol 2022;29(3):1496–7.
[47] Chang L, Wang Y, Wang Z, Xiao D, Song Q. Number of positive lymph nodes affects oncologic outcomes in cN0 mucoepidermoid carcinoma of the major salivary gland. Sci Rep 2024;14(1):9086.
[48] Rossi CR, Mozzillo N, Maurichi A, et al. The number of excised lymph nodes is associated with survival of melanoma patients with lymph node metastasis. Ann Oncol 2014;25(1):240–6.
[49] Swanson RS, Compton CC, Stewart AK, Bland KI. The prognosis of T3N0 Colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003;10(1):65–71.
[50] Neville HL, Andrassy RJ, Lobe TE, et al. Preoperative staging, prognostic factors, and outcome for extremity rhabdomyosarcoma: a preliminary report from the

intergroup rhabdomyosarcoma study IV (1991-1997). J Pediatr Surg 2000;35(2):317–21.
[51] La TH, Wolden SL, Rodeberg DA, et al. Regional nodal involvement and patterns of spread along in-transit pathways in children with rhabdomyosarcoma of the extremity: a report from the children's oncology group. Int J Radiat Oncol Biol Phys 2011;80(4):1151–7.
[52] Lobeck I, Dupree P, Karns R, Rodeberg D, von Allmen D, Dasgupta R. Quality assessment of lymph node sampling in rhabdomyosarcoma: a surveillance, epidemiology, and end results (SEER) program study. J Pediatr Surg 2017;52(4):614–7.
[53] Walterhouse D, Watson A. Optimal management strategies for rhabdomyosarcoma in children. Paediatr Drugs 2007;9(6):391–400.
[54] Routh JC, Dasgupta R, Chi YY, et al. Impact of local control and surgical lymph node evaluation in localized paratesticular rhabdomyosarcoma: a report from the children's oncology group soft tissue sarcoma committee. Int J Cancer 2020;147(11):3168–76.
[55] Bisogno G, De Salvo GL, Bergeron C, et al. Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2019;20(11):1566–75.
[56] Ketterl TG. Closing the gaps: progress in the care of adolescents and young adults with cancer. JCO Oncol Pract 2021;17(6):302–4.
[57] Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. CA Cancer J Clin 2020;70(6):443–59.
[58] Müller JA, Delank KS, Laudner K, et al. Clinical characteristics of sarcoma patients: a population-based data analysis from a German clinical cancer registry. J Cancer Res Clin Oncol 2023;149(19):17051–69.
[59] Kern L, Henssen A, Eggert A, Scheer M. The other site of rhabdomyosarcoma. Cancer Med 2024;13(20):e70348.
[60] Rohde J, Henssen A, Eggert A, Scheer M. Rhabdomyosarcoma of head and neck varies in aggressiveness depending on the specific site of origin. Oral Oncol 2025;164:107263.
[61] Zhang SL, Wang WR, Liu ZJ, Wang ZM. Marital status and survival in patients with soft tissue sarcoma: a population-based, propensity-matched study. Cancer Med 2019;8(2):465–79.
[62] Hawkins DS, Chi YY, Anderson JR, et al. Addition of vincristine and Irinotecan to vincristine, dactinomycin, and cyclophosphamide does not improve outcome for intermediate-risk rhabdomyosarcoma: a report from the children's oncology group. J Clin Oncol 2018;36(27):2770–7.
[63] Gupta AA, Xue W, Harrison DJ, et al. Addition of temsirolimus to chemotherapy in children, adolescents, and young adults with intermediate-risk rhabdomyosarcoma (ARST1431): a randomised, open-label, phase 3 trial from the children's oncology group. Lancet Oncol 2024;25(7):912–21.
[64] Pasquali S, Bonvalot S, Tzanis D, et al. Treatment challenges in and outside a network setting: soft tissue sarcomas. Eur J Surg Oncol 2019;45(1):31–9.
[65] Sandrucci S, Naredi P, Bonvalot S. Centers of excellence or excellence networks: the surgical challenge and quality issues in rare cancers. Eur J Surg Oncol 2019;45(1):19–21.
[66] Lopez-Beltran A, Canas-Marques R, Cheng L, Montironi R. Histopathologic challenges: the second OPINION issue. Eur J Surg Oncol 2019;45(1):12–5.