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Rhabdomyosarcoma of head and neck varies in aggressiveness depending on the specific site of origin

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ABSTRACT

Objective: To evaluate predictive impact of granular subsites of head/neck rhabdomyosarcoma in a cross-age evaluation of the population-based SEER-program.
Design: Data were obtained for cases 0–90+ years, newly diagnosed with rhabdomyosarcoma at head/neck, registered in SEER17 2000–2020. Disease-specific survival (DSS) and overall survival (OS) were the endpoints, using the Kaplan-Meier estimator and Cox proportional hazards regression model. A granular site categorization was established.
Results: Median age of 1114 cases was 11 years. 5-year OS and DSS were 59.1 %±3.1 (95 %CI) and 62.4 %±3.1 with median follow-up for 662 survivors of 8.6 years. Increasing age was independently associated with worse prognosis. The rate of affected subsites varied considerably. Age, histology, tumor size, disease stage, the proportion of pathologically examined and affected lymph nodes differed significantly according to granular subsite. Granular subsites were of independent predictive impact when adjusted for age, size, histology, stage, and pathological lymph node status. While rhabdomyosarcoma at orbit, parotid gland, and ear correlated with best survival, larynx, oral cavity, paranasal sinuses, brain, pharynx, and nose were associated with adverse survival. In contrast to all other subsites, nasal and paranasal sinus rhabdomyosarcoma were predominantly alveolar, large, distant spread, and with the highest proportion of affected lymph nodes. Rhabdomyosarcoma of nose/paranasal sinuses exhibit high potential of spreading not only suggesting different biology but thorough staging including pathological lymph node assessment.
Conclusion and Relevance: Granular head/neck subsites show different characteristics between subsites and highly varying outcomes. Understanding the impact of granular head/neck subsites on outcome may inform risk-adapted and novel approaches to rhabdomyosarcoma.

Introduction

Rhabdomyosarcoma (RMS) is a malignant soft-tissue sarcoma that commonly affects children and accounts for 4.5 % of all childhood cancers [1–3]. It originates from mesenchymal cells that show differentiation towards skeletal muscle[4,5] and includes embryonal, alveolar, pleomorphic, and spindle cell subtypes [6,7]. 30 %-40 % of pediatric RMS is found in the head/neck[8–10] while head/neck RMS in adults is relatively rare and survival is worse [11,12] RMS of the head and neck presents a unique treatment challenge. Although it is typically detected at an early stage and has a low metastatic potential compared to other RMS sites, the prognosis is moderate due to frequent infiltration of critical structures[13–19]. The feasibility of surgery is limited, necessitating radiation therapy as the primary local treatment modality. This can be particularly challenging in young children. Historically, in the preliminary report of the first pediatric Intergroup-Rhabdomyosarcoma-Study (IRS) starting enrolment in 1972, lesions in the head/neck represented the largest group (36 %) and were mostly unresectable [8]. In the following pediatric RMS trials, different outcomes were observed depending on the exact head/neck localization. Orbital RMS had significantly better outcomes than other head/neck subsites[20–22] whereas RMS involving the meninges, bony structures,

Abbreviations: RMS, (Rhabdomyosarcoma); PM, (parameningeal); nPM, (non-parameningeal); IRS, (Intergroup-Rhabdomyosarcoma Study); SEER, (Surveillance, Epidemiology, and End Results); NOS, (not otherwise specified); OS, (overall survival); DSS, (disease-specific survival); HIV, (human immunodeficiency virus).

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and cranial nerves had significantly worse outcomes [22,23]. As a result, the third IRS study protocol, which began enrollment in 1984, was the first to provide detailed recommendations for head/neck RMS in a more granular categorization [24]. The categorization of orbit, parameningeal (PM), and non-parameningeal (nPM), was established as a result of the pediatric IRS I-III trials[22–24,22–26] and is continually applied without change[25,27]. More recently, different prognoses of different subsites within these categorizations were reported [17,28,29].

The objective of this study is to assess frequencies of affected subsites, evaluate cross-age characteristics and predictive impact of granular subsites to enable adaptation of individual treatment aggressiveness and inform novel risk-adapted treatment approaches.

Methods

RMS cases were obtained from the November 2022 release of the Surveillance, Epidemiology, and End Results (SEER)[30] Program-17 (2000–2020), downloaded May 2023 (ICD-O-3 8900, 8901, 8902, 8912, 8920, 8921). Inclusion criteria were malignant behavior, known age, positive histology, and first malignant disease located at head/neck (figure 1). Death certificate cases were excluded.

To identify potential age-dependent differences in disease presentation we applied different age categorizations. To establish a meaningful site classification, we first applied the categorization of the international RMS stratification system (PM, nPM, orbit)[22–25] to the variable "primary site – labeled". All "Connective, subcutaneous, other soft tissue of the head, face, neck (C49.0)" were classified as head/neck not otherwise specified (NOS). To further determine prognostic effects, a granular classification was applied: orbit, ear, nose, sinuses, oral cavity, parotid gland, pharynx, larynx, brain, bones, and skin/connective tissue. A detailed description of all selected variables is presented in the data supplement (online only).

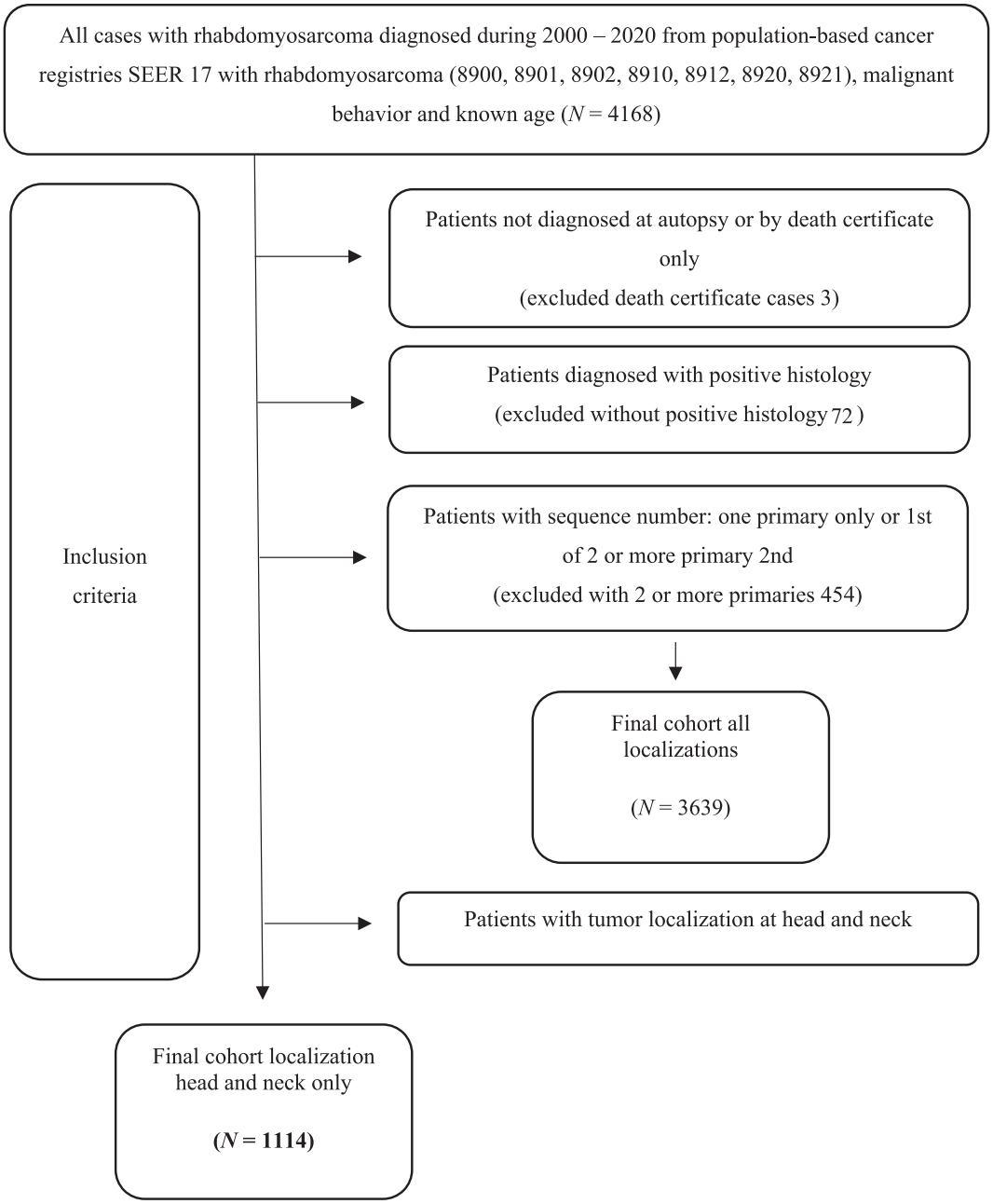

Fig. 1. Final cohort inclusion criteria.

Statistical methods

Statistical analysis was conducted using IBM SPSS®29 (Armonk, New York, U.S.). Overall survival (OS) and disease-specific survival (DSS) were calculated using the Kaplan-Meier estimator[31]. The endpoints were death from any cause (OS) and death from RMS (DSS). Time from diagnosis to death or last follow-up was used for OS and DSS. Patients without event were censored at last follow-up. Patients with unknown cause of death (unclear if death was due to disease or other reasons) were excluded from DSS analysis. Confidence intervals (CI) were calculated using Greenwood́s formula[32] presented at 95 % level. The log-rank test was used for comparison. The Cox proportional hazards regression method was used to analyze the independent effects of potential prognostic factors. Distribution of characteristics were analyzed with the Chi^2-test.

Results

Characteristics

A total of 1114 cases of head/neck RMS from 2000 to 2020 were identified. Gender distribution showed slight male preponderance with 618 (55 %) males. The median age was 11 years (range 0–90 +). 713 (64 %) patients were 0–17 years, 207 (19 %) were 18–39 years, 137 (12 %) were 40–64 years and 57 (5 %) were ≥ 65 years. Granular age categorizations, especially for pediatric patients, are presented in Table 1, figure 2.

The most affected subsites were 98 (9 %) nose, 183 (16 %) paranasal sinus, 108 (10 %) pharynx, and 453 (41 %) skin/connective tissue beside 155 (14 %) orbital tumors. Less commonly affected subsites included 13 (1 %) ear (12 coded as “C30.1 middle ear”, 1 as “C44.2 external ear”), 53 (5 %) oral cavity, 11 (1 %) parotid gland, 8 (1 %) larynx, 18 (2 %) brain, and 14 (1 %) bones (8 coded as “C41.1-Mandible”, 6 as “C41.0-Bones of skull and face and associated joints”).

Tumors were ≤ 3 cm in 203 (18 %), 3,1–5 cm in 288 (26 %), and > 5 cm in 277 (25 %) (346 no size documented).

In 498 (45 %) tumors rhabdomyosarcoma histology was embryonal, in 354 (32 %) alveolar, 38 (3 %) spindle cell, 27 (2 %) pleomorphic (adult type), 10 (1 %) mixed type, 4 (<1%) RMS with ganglionic differentiation, and 183 (16 %) RMS NOS.

Lymph Nodes and tumor stage

In 186 (17 %) patients regional lymph nodes were pathologically examined, while in 865 (78 %) no examination of regional lymph nodes was performed (63 unknown) (Table 1, figure 2). Detailed information on the number of examined and positive lymph nodes is presented in the appendix. For 450 (40 %) patients the tumor stage was regional, for 311 (28 %) localized, and for 304 (27 %) distant.

Distribution of characteristics according to age and site

Age, histology, granular tumor site, stage, pathological lymph node examination, and lymph node status differed according to granular subsite (figure 3, Supplementary Table S2): 155 orbital RMS were predominantly pediatric, mainly non-alveolar histology, ≤3cm, localized stage. A small minority of lymph nodes were pathologically examined (2/3 lymph nodes positive). Of 8 larynx RMS, 87.5 % were ≥ 18 years with most tumors ≤ 3 cm, non-alveolar, and localized stage. Pharynx RMS (108) were mostly found in 4–9 year-olds (39.8 %) mainly 3,1–5 cm, non-alveolar with regional spread. Fifteen/19 examined lymph nodes were positive. Eleven parotid gland RMS occurred at any age, while most were 10–17 years. All tumors were > 3 cm, mostly non-alveolar and regional. Nearly all 13 ear RMS were pediatric, aged 4–9 years (with one exception > 65 years) and predominantly regional, 2 cases exhibited distant metastases. Oral cavity RMS (53) occurred at all ages, mostly in 4–9 and 18–39 year-olds, were mainly localized, while 12 distant stages were reported. Eighteen brain RMS occurred in all ages (most in 3 and 18–39-year-olds), were mainly non-alveolar and localized or regional stage. Fourteen bone RMS were mostly reported in 4–9 year-olds (50 %), 3.1–5 cm, and all had non-alveolar histology; 36 % were localized, while 35.7 % distant metastases were reported.

In contrast, 183 paranasal sinus RMS and 98 nose RMS occurred at all ages, were mainly alveolar, and sized > 5 cm. Paranasal sinus RMS were mostly regional (58 %), 34 % were of distant stage. Nose RMS were 63.3 % distant stage. Most lymph nodes were not pathologically examined, while 42/44 (96 %) lymph nodes in paranasal sinus RMS and 18/20 in nose RMS were positive (figure 3, Supplementary Table S2).

The vast majority were 453 RMS of skin/connective tissue, spread across all age groups, mostly in 4–9 year-olds. Most tumors are > 5 cm, with non-alveolar histology, and regional spread. Prognostic factors differed according to age.

Outcome

5-year OS and DSS rates were 59.1 %±3.1 (95 %CI) and 62.4 %±3.1. At last follow-up, 662 (59 %) patients were alive. Median follow-up for survivors was 8.75 years. For 394 patients who died due to disease, median time to death was 1.5 years.

Factors for overall survival and disease-specific survival

Results of univariate analyses are shown in Table 1. No significant difference in DSS and OS for female and male patients were observed. Pediatric patients had significantly better DSS and OS. Patients aged 3–9 had the best DSS and OS (82.5 %, 80.4 %). For adults, ages 18–39 and 40–64 years were associated with adverse DSS. Survival seemed to be slightly better after the age of 65 years, while OS might overlap with other causes of death. When evaluating the year of diagnosis, both DSS and OS showed no improvement. RMS patients with the primary site being orbit showed best survival with a 5-year DSS and OS of 90.2 %, respectively. DSS and OS of the PM site were significantly worse, with 45.6 % and 43.2 %. According to granular site classification, patients with RMS at orbit, parotid gland, and bones had the best 5-year DSS and OS. Significantly adverse survival rates were observed in the brain, paranasal sinus, and nose. Tumor sizes 3.1–5 cm and > 5 cm were associated with adverse DSS and OS. The highest 5-year survival rates showed the embryonal RMS subtype with 77.7 % (DSS) and 76.2 % (OS) while the lowest observed 5-year survival rates were 43.8 % (DSS) and 40.6 % (OS) for alveolar RMS. Survival was best in localized stage, followed by regional stage. Upon closer examination of the regional stage, direct extension was associated with better DSS and OS than regional lymph node involvement. Patients with positive regional lymph nodes had 5-year survival rates of 40.1 % (DSS) and 37.2 % (OS). Patients with pathologically negative regional lymph nodes showed the best survival with 70.6 % (DSS) and 68.3 % (OS). The worst 5-year survival was observed in patients with unknown lymph node status. The number of pathologically examined lymph nodes was evaluated. We could observe a slight trend towards better survival probability for patients with 3 examined lymph nodes compared to those with 1 or 2 examined lymph nodes. Lymph node biopsy and aspiration were associated with adverse DSS.

Cox regression analysis

To establish age-spanning independent prognostic significance, patient’s age, tumor size, histology, stage, pathological lymph node status, and primary site classified according to the IRS-system were included in a multivariable model (Table 2). In a second model, the granular site classification was included.

Both site classifications were of independent significance when adjusted for age, histology, site, size, and lymph node status. Age,

Table 1
Univariate analysis of patient and tumor characteristics in 1114 patients with RMS of the head/neck.

	N	(%)	5yrs OS (%)	95 %CI	p value	N	(%)	5yrs DSS (%)	95 % CI	p value
All Patients	1114	100 %	59.10 %	±3.1		1104	100 %	62.40 %	±3.1	
Sex					0.18					0.246
female	496	45 %	61.30 %	±4.51		492	45 %	64.50 %	±4.51	
male	618	55 %	57.30 %	±4.11		612	55 %	60.50 %	±4.11	
Age [years]					**<0.001**					**<0.001**
<1	35	3 %	72.50 %	±15.29		35	3 %	72.50 %	±15.29	
1	36	3 %	73.10 %	±15.09		35	3 %	75.40 %	±14.9	
2	51	5 %	69.10 %	±13.13		50	5 %	70.50 %	±13.13	
3	68	6 %	74.60 %	±10.98		67	6 %	79 %	±10.19	
4-9	307	28 %	81.80 %	±4.51		307	28 %	83.30 %	±4.51	
10-17	216	19 %	65.60 %	±6.66		214	19 %	67.70 %	±6.66	
≥18	401	36 %	30.20 %	±5.10		396	36 %	33.70 %	±5.29	
Age [years]					**<0.001**					**<0.001**
0–17	713	64 %	74.30 %	±3.33		708	64 %	76.20 %	±3.33	
18–39	207	19 %	33.50 %	±7.25		204	18 %	34.70 %	±7.45	
40–64	137	12 %	27.40 %	±8.04		135	12 %	30.50 %	±8.82	
≥65	57	5 %	25.60 %	±12.35		57	5 %	39.30 %	±14.5	
Age [years]					**<0.001**					**<0.001**
<1	35	3 %	72.50 %	±15.29		35	3 %	72.50 %	±15.29	
1-2	87	8 %	70.70 %	±9.8		85	8 %	72.50 %	±9.8	
3-9	375	34 %	80.40 %	±4.31		374	34 %	82.50 %	±4.12	
10-17	216	19 %	65.60 %	±6.66		214	19 %	67.70 %	±6.66	
18–39	207	19 %	33.50 %	±7.25		204	19 %	34.70 %	±7.45	
40–65	139	12 %	27.30 %	±8.04		137	12 %	30.40 %	±8.82	
>65	55	5 %	25.40 %	±12.35		55	5 %	39.30 %	±14.7	
Primary site					**<0.001**					**<0.001**
orbit	155	14 %	90.20 %	±4.9		155	14 %	90.20 %	±4.9	
HN-nPM	98	9 %	65.7 %	±10.19		98	9 %	68 %	±10.19	
HN-PM	411	37 %	42.5 %	±5.1		406	37 %	44.9 %	±5.29	
HN NOS	450	40 %	61.80 %	±4.7		445	40 %	66.40 %	±4.7	
Granular site					**<0.001**					**<0.001**
orbit	155	14 %	90.20 %	±4.9		155	14 %	90.20 %	±4.9	
parotid gland	11	1 %	90 %	±18.62		11	1 %	90 %	±18.62	
bones[*]	14	1 %	88.90 %	±20.58		14	1 %	100 %	±0	
ear[*a]	13	1 %	76.90 %	±22.93		13	1 %	83.90 %	±20.38	
oral cavity	53	5 %	64.60 %	±13.72		53	5 %	64.60 %	±13.72	
skin/connective tissue	453	41 %	61.80 %	±4.7		448	41 %	66.50 %	±4.7	
pharynx	108	10 %	58.40 %	±10		107	10 %	60.20 %	±10	
larynx	8	1 %	62.50 %	±33.52		8	1 %	62.50 %	±33.52	
nose	98	9 %	37.70 %	±9.8		97	9 %	40 %	±10.98	
paranasal sinus	183	16 %	33.20 %	±7.45		180	16 %	35.70 %	±7.64	
brain	18	2 %	26.80 %	±23.32		18	2 %	28.40 %	±24.5	
Tumor size [cm]					**<0.001**					**<0.001**
≤3	203	18 %	80.60 %	±5.68		202	18 %	82.80 %	±5.49	
3.1–5	288	26 %	66.70 %	±5.88		286	26 %	69.30 %	±5.68	
>5	277	25 %	51 %	±6.27		273	25 %	54.70 %	±6.47	
unkonwn/not reported	346	31 %	46.70 %	±5.49		343	31 %	49.80 %	±5.68	
Histological type					**<0.001**					**<0.001**
alveolar	354	32 %	40.60 %	±5.49		346	31 %	43.80 %	±5.68	
embryonal	498	45 %	76.20 %	±3.92		497	45 %	77.70 %	±3.92	
pleomorphic (adult type)	27	2 %	28.30 %	±18.03		27	2 %	44.30 %	±20.58	
mixed type	10	1 %	56.30 %	±32.34		10	1 %	56.30 %	±32.34	
spindle cell	38	3 %	83.80 %	±13.33		38	3 %	72.90 %	±20.19	
ganglionic differentiation	4	0 %	50 %	±49		4	0 %	50 %	±49	
RMS NOS	183	16 %	47.80 %	±8.04		182	16 %	52.10 %	±8.23	
Stage					**<0.001**					**<0.001**
localized	311	28 %	85 %	±4.12		311	28 %	87.30 %	±3.92	
regional	450	40 %	58.10 %	±4.70		447	40 %	60.90 %	±4.90	
distant	304	27 %	34.40 %	±5.88		299	27 %	37.30 %	±6.08	
unknown/unstaged	49	4 %	49.80 %	±15.68		47	4 %	55.90 %	±16.66	
Stages classified					**<0.001**					**<0.001**
localized	311	28 %	85 %	±4.12		311	28 %	87.30 %	±3.92	
regional NOS	152	14 %	57.50 %	±9.02		152	14 %	58.30 %	±9.02	
regional direct extension and lymph node involvement	79	7 %	51 %	±11.17		78	7 %	56.30 %	±11.56	
regional direct extension only	190	17 %	60.60 %	±7.06		188	17 %	64 %	±7.06	
regional lymph node involved only	29	3 %	61.70 %	±17.84		29	3 %	61.70 %	±17.84	
distant	304	27 %	34.40 %	±5.88		299	27 %	37.30 %	±6.08	
unknown/unstaged	49	4 %	49.80 %	±15.68		47	4 %	52.40 %	±17.05	
Path. lymph node status					**<0.001**					**<0.001**
positive	123	11 %	37.20 %	± 9.21		121	11 %	40.10 %	± 9.6	
negative	69	6 %	68.30 %	± 11.98		68	6 %	70.60 %	±11.96	
no examination	865	78 %	63.10 %	± 3.33		859	78 %	66.20 %	± 3.33	

(*continued on next page*)

Table 1 (*continued*)

	N	(%)	5yrs OS (%)	95 %CI	p value	N	(%)	5yrs DSS (%)	95 % CI	p value
unknown	57	5 %	33.80 %	± 13.72		56	5 %	35.80 %	± 14.5	
Number of positive regional nodes					**<0.001**					**<0.001**
all nodes examined are negative	69	6 %	68.30 %	±11.96		68	6 %	70.60 %	±11.96	
1 node is positive	44	4 %	48.60 %	±15.09		44	4 %	48.60 %	±15.09	
2 nodes are positive	6	1 %	33.30 %	±37.63		6	1 %	33.30 %	±37.63	
3 or 4 nodes are positive	4	0 %	33.30 %	±53.31		4	0 %	33.30 %	±53.31	
≥5 nodes are positive	9	1 %	20.8 %[*b]	±33.52		9	1 %	20.8 %[*c]	±33.52	
positive aspiration of lymph nodes was performed	44	4 %	30.10 %	±16.46		43	4 %	32.80 %	±17.84	
positive lymph nodes, number is unspeicified	16	1 %	31.30 %	±22.74		15	1 %	42.40 %	±26.46	
no examination	865	78 %	63.10 %	±3.33		859	78 %	66 %	±3.33	
unknown	57	5 %	33.80 %	±13.72		56	5 %	35.80 %	±14.5	
Path. lymph node examination					**<0.001**					**<0.001**
yes	186	17 %	47.10 %	±7.84		184	17 %	49.60 %	±7.84	
no	865	78 %	63.10 %	±3.33		859	78 %	66 %	±3.33	
unknown	63	6 %	39.60 %	±13.13		61	6 %	42.40 %	±13.72	
Number of examined regional nodes					**<0.001**					**<0.001**
no nodes were examined	865	78 %	63.10 %	±3.33		859	78 %	66 %	±3.33	
1 node was examined	57	5 %	55.50 %	±12.94		57	5 %	56.50 %	±13.13	
2 nodes were examined	16	1 %	65 %	±24.86		16	1 %	65 %	±24.89	
3 nodes were examined	7	1 %	85.70 %	±25.87		7	1 %	85.70 %	±25.87	
4 nodes were examined	3	0 %	66.70 %	±53.31		3	0 %	66.70 %	±53.31	
5 nodes were examined	4	0 %	50 %	±49		4	0 %	50 %	±49	
≥6 nodes were examined	30	3 %	28.40 %	±21.17		29	3 %	29.70 %	±27.83	
aspiration of regional nodes	50	4 %	24.60 %	±14.5		49	4 %	26.50 %	±15.48	
lymph smapling (number is unknown)	3	0 %	100 %	±0		3	0 %	100 %	±0	
lymph node deissection (number is unknown)	3	0 %	66.70 %	±53.31		2	0 %	100 %	±0	
surgical lymph node removal (number is unknown)[*d]	19	2 %	47.20 %	±23.72		19	2 %	56.30 %	±24.7	
unknown	57	5 %	33.80 %	±13.72		56	5 %	35.80 %	±14.5	
Year of diagnosis										
patients ≤18 years:	728	100 %			0.481	723	100 %			0.255
2000 – 2005	230	32 %	74.2%	± 5.68		230	32 %	74.2%	±5.68	
2006 – 2010	178	24 %	69.5%	± 6.86		175	24 %	71 %	±6.86	
2011 – 2015	173	24 %	76.5%	± 6.47		171	24 %	78.6%	±6.27	
2016 – 2020	147	20 %	78.5%	± 8.82		147	20 %	83.3%	±7.84	
patients > 18 years:	386	100 %			0.678	381	100 %			0.52
2000 – 2005	78	20 %	27.4%	±10.19		77	20 %	28.4%	±10.39	
2006 – 2010	101	26 %	32 %	± 9.21		100	26 %	36.9%	±9.8	
2011 – 2015	90	23 %	28.2%	± 9.41		88	23 %	32.5%	±20.58	
2016 – 2020	117	30 %	32.8%	± 12.15		116	30 %	38.3%	±13.33	

[*] bones (thereof 8 coded as "C41.1-Mandible" and 6 as "C41.0-Bones of skull and face and associated joints").
[*a] ear (thereof 12 coded as "C30.1 middle ear", 1 "C44.2 external ear").
[*b] last follow up at 3,75 years.
[*c] last follow up at 3,75 years.
[*d] and not documentated as a sampling or dissection; nodes were examined, but the number is unknown.

histology, and stage were of independent prognostic significance. In the model with granular site classification survival of RMS at the parotid gland, bones, and ear did not significantly differ from the reference orbit. RMS at oral cavity, pharynx, nose, and paranasal sinus, were independently associated with adverse DSS beside the less specified skin/connective tissue. Larynx and brain RMS were associated with borderline adverse DSS. All mentioned subsites were associated with significantly adverse OS. Cases with RMS at larynx, oral cavity, and paranasal sinus had the highest hazard ratio for adverse OS and DSS. Patients in the pediatric age (0–17 years) had best outcomes. Hazard ratio increases with age (OS, DSS). Undocumented tumor size correlated with adverse survival. Alveolar histology correlated with adverse OS/DSS. While there was no distinction between positive and negative lymph nodes, the documentation of "unknown" lymph node involvement was independently associated with adverse OS/DSS.

Discussion

In this age-spanning cohort study of 1114 head/neck rhabdomyosarcoma based on SEER-17 from 2000 to 2020, we found that the prevalence of individual RMS head and neck subsites varies significantly according to age and is prognostically distinct when adjusted for patient age, tumor size, rhabdomyosarcoma subtype, disease stage, and pathological lymph node involvement.

Sites with the best DSS were orbit (90.2 %), parotid gland (90 %) and ear (83.9 %), while oral cavity, paranasal sinus, and larynx had the highest hazard ratios for adverse DSS. In this cross-age cohort, OS and DSS at 5 years were 59.1 %±3.1 (95 %CI) and 62.4 %±3.1, respectively. Survival did not improve during the period analyzed for either adult or pediatric patients.

Patient's age, tumor size, RMS subtype, disease stage, pathological lymph node involvement, and examination differed according to granular site. In contrast to all other subsites, nose and paranasal sinus RMS were predominantly alveolar, >5cm with highest rates of distant spread disease. Most distant metastases originated from the nose (63 %). Both subsites exhibited the highest rates of positive lymph nodes when pathologically examined (up to 96 %). Individual head/neck subsites were affected at different frequencies depending on age. While orbital, ear, pharynx and parotid gland RMS were predominantly affected in pediatric age, paranasal sinus, nose and oral cavity RMS occurred at all ages and larynx RMS predominantly at ≥ 18 years.

Age was an independent prognostic factor with poorer prognosis with increasing age. Most patients fell within the pediatric age group ≤ 17 years (64 %) with the majority being 4–9 years. In literature, most head/neck RMS are reported at 1–4 years[33], 0–6 years[8,34], and 0–5 years[35]. We applied different age classifications for potential future

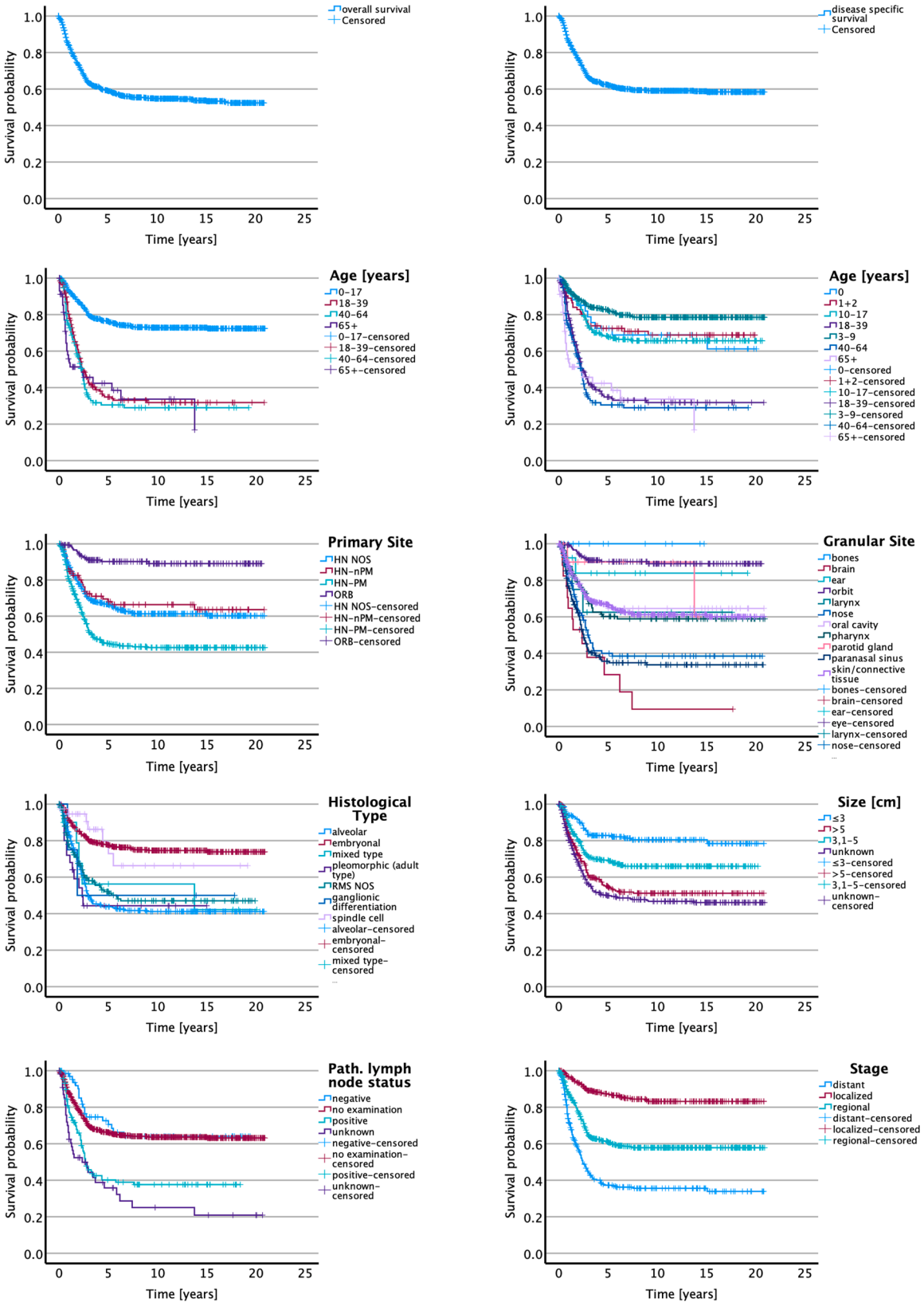

Fig. 2. Overall and Disease-Specific survival of 1114 patients with RMS of head/neck. Disease-specific survival according to age, site, histology, size, pathological lymph node status and stage.

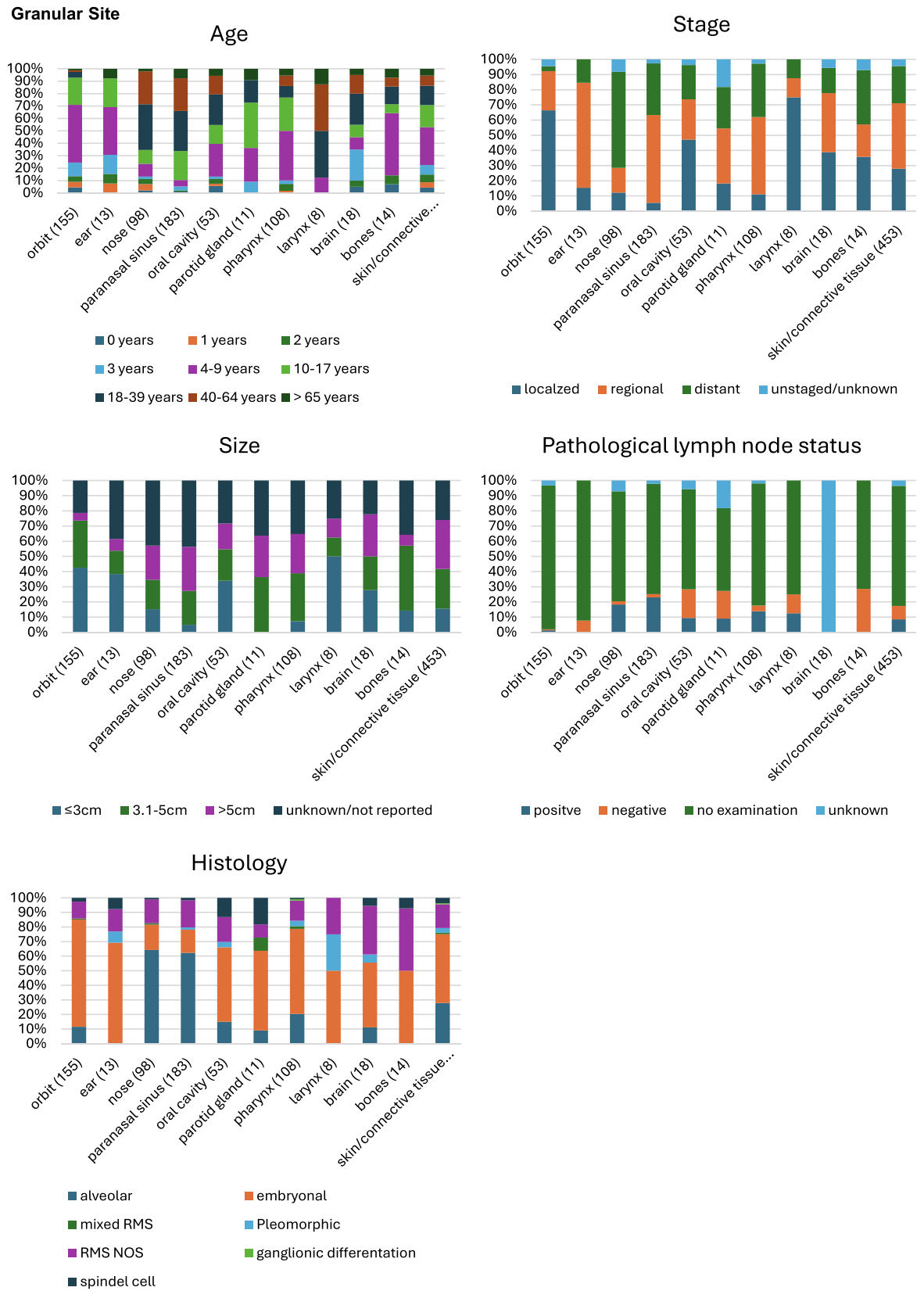

Fig. 3. Distribution of Characteristics according to granular site and age. Stage varies according to the primary site and age. The rate of metastases increases with age from 18 years and decreases from 65 years. 43.5% of people aged 18–39 have metastases, slightly falling to 39.4% for those aged 40–64 and 24.6% for those aged 65 and above. The primary site differs according to histology, stage, and lymph node status. Most distant metastases originate from the nose (63%).

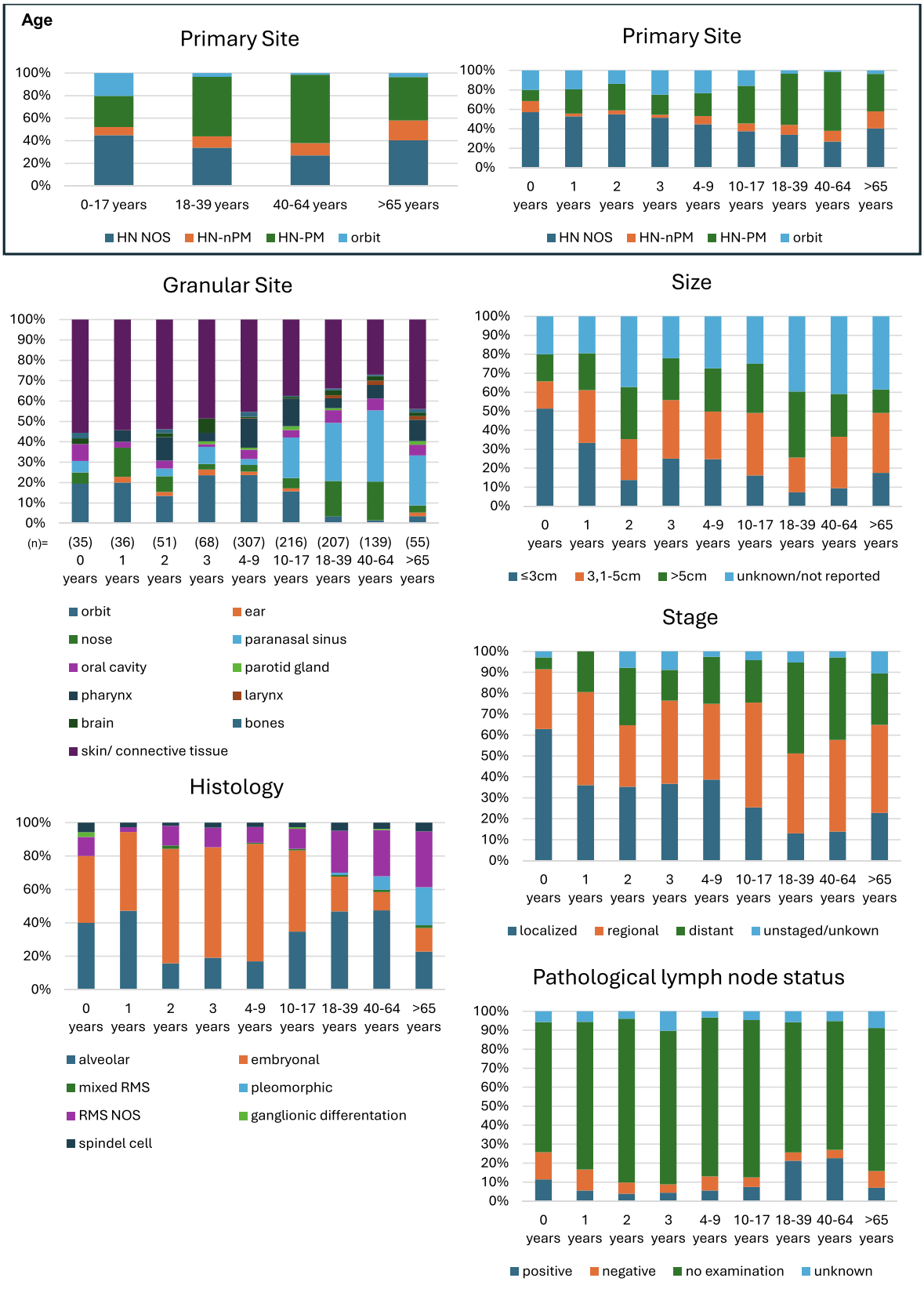

Fig. 3. (*continued*).

use in cross-age study designs. 4–9-year-old patients had best survival (83.3 % at 5 years). In the pediatric international RMS risk stratification ≥ 10 years is the cut-off[36,37] while in pediatric RMS better survival was seen in < 15 years [13].

According to the internationally consented definition of RMS sites within pediatric RMS protocols head/neck is subdivided into orbit, PM, and nPM[22–25,37–43]. Our analysis's most reported site was PM (38 %), followed by orbit (14 %). According to literature, pediatric head/

Table 2
Multivariate analysis.

	Overall Survival				Disease Specific Survival			
	Hazard Ratio	95 % CI Lower	95 % CI Upper	*p*-value	Hazard Ratio	95 % CI Lower	95 % CI Upper	*p*-value
Age [years]								
0–17	1.0				1.0			
18–39	2.265	1.759	2.919	***<0.001***	2.222	1.706	2.894	***<0.001***
40–64	3.200	2.438	4.193	***<0.001***	2.926	2.189	3.911	***<0.001***
≥65	8.081	5.603	11.656	***<0.001***	5.636	3.647	8.710	***<0.001***
Primary site								
orbit	1.0				1.0			
HN-nPM	2.945	1.541	5.627	***0.005***	2.752	1.368	5.535	***0.009***
HN-PM	2.801	1.583	4.959	***<0.001***	2.748	1.487	5.007	***0.001***
HN NOS	3.311	1.877	5.842	***<0.001***	2.917	1.582	5.378	***<0.001***
Tumor size [cm]								
≤3	1.0				1.0			
3.1–5	0.934	0.646	1.351	*0.851*	1.040	0.691	1.564	*0.859*
>5	1.253	0.873	1.799	*0.126*	1.366	0.916	2.037	*0.131*
Unknown/Not reported	1.539	1.087	2.178	***0.008***	1.686	1.147	2.478	***0.008***
Histological type								
non-alveolar	1.0				1.0			
alveolar	1.392	1.128	1.710	***0.006***	1.371	1.097	1.714	***0.006***
pleomorphic	1.108	0.654	1.875		1.025	0.547	1.923	
				0.938				*0.935*
Stage								
localized	1.0				1.0			
regional	2.094	1.527	2.871	***<0.001***	2.320	1.627	3.308	***<0.001***
distant	3.490	2.500	4.873	***<0.001***	3.869	2.670	5.606	***<0.001***
Path. LN status								
negative	1.0				1.0			
no examination	1.009	0.659	1.546	*0.776*	1.072	0.666	1.726	*0.805*
positive	1.021	0.632	1.649	*0.740*	1.094	0.645	1.855	*0.764*
unknown	3.583	1.992	6.447	***<0.001***	4.027	2.148	7.50	***<0.001***
Age [years]								
0–17	1.0				1.0			
18–39	2.268	1.749	2.940	***<0.001***	2.200	1.676	2.887	***<0.001***
40–64	3.126	2.354	4.153	***<0.001***	2.794	2.064	3.783	***<0.001***
≥65	7.960	5.479	11.565	***<0.001***	5.565	3.577	8.658	***<0.001***
Site classification								
orbit	1.0				1.0			
parotid gland	1.273	0.165	9.824	*0.817*	1.282	0.164	10.003	*0.813*
bones	1.123	0.249	5.073	*0.880*	/*	0.0	∞	*0.934*
ear	2.241	0.636	7.896	*0.209*	1.632	0.362	7.366	*0.524*
oral cavity	3.097	1.494	6.416	***0.002***	3.388	1.585	7.240	***0.002***
skin/connective tissue	3.307	1.866	5.859	***<0.001***	2.909	1.572	5.383	***<0.001***
pharynx	2.781	1.478	5.234	***0.002***	2.671	1.360	5.247	***0.004***
larynx	3.544	1.137	11.044	***0.029***	3.568	0.979	13.003	*0.054*
nose	2.392	1.252	4.571	***0.008***	2.340	1.172	4.670	***0.016***
paranasal sinus	3.159	1.727	5.776	***<0.001***	3.218	1.687	6.139	***<0.001***
brain	2.726	1.095	6.789	***0.031***	2.598	0.997	6.768	*0.051*
Tumor size [cm]								
≤3	1.0				1.0			
3.1–5	0.936	0.644	1.360	*0.729*	1.044	0.691	1.578	*0.838*
>5	1.227	0.851	1.769	*0.274*	1.329	0.887	1.992	*0.164*
unknown/not reported	1.512	1.063	2.150	***0.022***	1.655	1.120	2.446	***0.012***
Histological type								
non-alveolar	1.0				1.0			
alveolar	1.341	1.078	1.668	***0.008***	1.302	1.032	1.642	***0.026***
pleomorphic	1.090	0.643	1.848	*0.749*	1.007	0.536	1.892	*0.982*
Stage								
localized	1.0				1.0			
regional	2.090	1.514	2.887	***<0.001***	2.348	1.633	3.376	***<0.001***
distant	3.673	2.613	5.164	***<0.001***	4.167	2.854	6.084	***<0.001***
Path. LN status								
negative	1.0				1.0			
no examination	0.953	0.621	1.462	*0.826*	1.002	0.623	1.613	*0.992*
positive	0.960	0.593	1.553	*0.867*	1.013	0.597	1.718	*0.962*
unknown	3.383	1.648	6.945	***<0.001***	3.818	1.779	8.194	***<0.001***

* not determinable; Bold values indicate statistical significance $p < 0.05$.

neck RMS are distributed across various sites, such as orbit, nose[33,34], and paranasal sinus[34,38] whereas parotid gland[33,34], buccal mucosa, palate, larynx[33], and facial soft tissue are less commonly affected[34]. In adult RMS paranasal sinuses[39] and nasopharynx/nasal cavity are most commonly affected[39,40].

To elucidate cross-age differences between individual subsites we applied a granular categorization. Paranasal sinus (16 %) and orbit (14 %) were the most frequently affected subsites besides the less specified

subsite "skin/connective tissue". The sites with the best DSS were orbit (90.2 %), parotid (90 %), ear (83.9 %), bone (100 %). The best results in this series were reported for bone with no deaths. Isolated cases of primary bone RMS in head/neck are described in literature [44,45]. In contrast, bony erosion in soft tissue head/neck RMS results in worse prognosis and therefore risk-stratification in a higher-risk group [17]. In this cross-age series, hazard ratios of parotid gland (HR 1.282), ear (HR 1.632), and bone do not significantly differ from orbit. In contrast, oral cavity, paranasal sinus, brain, and larynx (HR 3.568) had the highest hazard ratio for adverse DSS. In a previous pediatric subsite evaluation of merely PM-RMS, paranasal sinus, infratemporal, and pterygopalatine fossa showed worst outcomes[17], while in a another pediatric evaluation of only nPM-subsites, they remained without prognostic difference [17,28].

When applying the international pediatric RMS site classification, orbital tumors had the best survival (DSS 90.2 %), followed by nPM (68.8 %). It was considerably worse in PM origin (45.6 %) in accordance with literature [17,29,35,36]. Interestingly, no prognostic differences were evident between nPM and PM RMS after adjustment for other risk factors. However, 450 cases coded as "C49.0-Conn, subcutaneous, other soft tissue: head, face, neck" and consequently analyzed as a separate group (HN-NOS) may limit informative value. Nevertheless, it raised the question: Are pediatric classifications appropriate for adult patients or cross-age stratifications?

It is questionable whether findings from pediatric studies can be applied to adults and vice versa. Cross-age evaluations are complicated not only due to different stratification systems but also due to differing participation in pediatric or internal medicine trials. While a population-based registry may present certain limitations, it remains an effective method for addressing cross-age issues. Given the limitations of local treatment procedures for different age groups, it may be rational to adopt varied approaches for specific subsites and age groups, taking into account the distinct aggressiveness of each subsite. Depending on the unique challenges associated with different head/neck subsites across various age groups, the implementation of distinct age categorizations may be beneficial.

Considering head/neck subsites in a granular classification is important to adapt individual treatment aggressiveness. Lymph node involvement and disease stage correlated with granular sites suggesting a different spreading potential for specific subsites.

In this series, there was no prognostic difference between pathologically positive and negative lymph nodes when adjusting for other factors. This suggests that adequate treatment might result in similar outcomes and underlines the crucial need for thorough and complete staging examinations. This is supported by the fact that patients with unknown lymph node involvement had independently worst outcomes (35.8 %), suggesting that lymph node involvement might not have been effectively treated. In an adult RMS *meta*-analysis primary lymph node involvement doubled the risk of distant metastasis [46].

In this series, 44 % of tumors were $\leq$ 5 cm and 25 % >5cm. Differing size categorizations complicate direct comparisons with other series [13,28,37,39,40,42]. Embryonal was the most frequent histology (45 %), followed by alveolar (32 %). RMS subtypes differed according to age. While pediatric patients had the highest proportion of embryonal RMS, alveolar was highest in 18–39 and 40–64 years. The distribution of RMS histology at head/neck compared to overall distribution in literature was similar [42,46]. In this series, most cases (40 %) were regionally spread. Disease stages differed according to age. Pediatric patients exhibited the highest rates of localized disease, while 18–64 year-olds had a distant disease rate of 39–43 %. The proportion of regionally spread disease remained consistent. Comparisons were limited since most pediatric patients are included in trials, referring to either localized or metastatic disease [47,48]. Therefore, this population-based cohort provides comprehensive unbiased overview. In this series, most patients did not undergo pathological lymph node examination. Among 186 patients with pathological examination of regional lymph nodes, 123 were positive. In literature, most pediatric lymph nodes are not affected [37]. For adults, literature shows a balanced distribution [39].

One limitation of this evaluation lies in the epidemiologic nature of the dataset itself. Regarding the site categorization, we were not able to make an exact allocation for C44.3, C44.4, and C49.0. Consequently, they were categorized as head/neck-NOS. Specifically, in the context of pathological lymph node analysis, no information about imaging was provided. Nevertheless, suspicious lymph nodes without pathological examination might have been classified as affected by imaging resulting in SEER-stage regional.

In summary, the various subsites exhibited a differential prevalence, with varying frequencies observed at different ages. They were prognostically distinct when adjusted for age, size, histology, stage, and pathological lymph node involvement. Specifically, RMS at oral cavity, pharynx, nose, and paranasal sinus were independently associated with adverse DSS besides the less specified skin/connective tissue. Larynx and brain were associated with borderline adverse DSS. All those subsites were associated with significantly adverse OS. In contrast to all other subsites, nasal and paranasal sinus RMS were predominantly alveolar, had larger size, highest rate of distant spread disease, and highest proportion of positive lymph nodes when pathologically analyzed. Rhabdomyosarcoma of nose/paranasal sinuses exhibit high potential of spreading not only suggesting different biology but thorough staging including pathological lymph node assessment. Based on these results we recommend considering the specific areas of the head/neck separately in detailed classification. This cross-age analysis revealed the necessity for the development of a novel more granular classification for head/neck sites. Given the varied challenges posed by different subsites, it may be advantageous to consider the development of age-specific categorizations. It is imperative to take into account the unique characteristics of each age group during the therapeutic process. By defining the predictive impact of granular subsites this study might enable the adaptation of individual treatment aggressiveness and inform novel risk-adapted treatment approaches. Given the observed heterogeneity in metastatic tendencies among different subsites, comprehensive biological research is imperative to inform effective therapeutic strategies.

CRediT authorship contribution statement

Juliane Rohde: Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft. **Anton Henssen:** Writing – review & editing. **Angelika Eggert:** Supervision, Writing – review & editing. **Monika Scheer:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2025.107263.

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