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Head and Neck Sarcomas: The UCLA Experience

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Abstract

Purpose—To profile the clinical presentation, subtype distribution, and treatment results of sarcomas of the head and neck at a single tertiary academic center over an 11-year period.

Materials and Methods—A retrospective review was performed by examining the records and reviewing the pathology of 186 patients with head and neck sarcomas treated at UCLA Medical Center from 2000 to 2011.

Results—The mean age of the study population was 49 +/− 22 years. 58% of the patients were male and 42% were female. Median duration of follow-up for the entire group was 18.5 months. The most common presenting symptom was a mass lesion in 59.9% of patients. The nasal cavity/sinus was the most common presenting site seen in 22% of patients. Solitary fibrous tumor/hemangiopericytoma was the most common subtype. 15% of patients had evidence of prior radiation exposure. 26.3% of tumors were greater than 5cm and 35.5% were high-grade. Margins were positive in 31.2% of patients. Lymph node metastasis was rare at 6.5%. Perineural invasion was identified in 6.5%. Among all subtypes, 5-yr recurrence-free survival and overall survival were 50% and 49%, respectively. Multivariate analysis demonstrated that grade and margin status were predictors of recurrence-free survival while grade and age affected overall survival.

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Conclusions—Head and neck sarcomas are a rare entity frequently presenting as a mass lesion. In our series, lesions tended to be high-grade with a significant portion of surgical specimens having positive margins. Grade and margin status were the most important predictors of survival.

Introduction

The management of sarcomas of the head and neck remains a challenge in the field of head and neck oncology. As sarcomas comprise less than 1% of all head and neck malignancies [1], there are no prospective, randomized-controlled trials to guide management. Current guidelines are based on the collective efforts of retrospective studies from tertiary-care centers as well as treatment guidelines extrapolated from sarcomas of the trunk and extremities.

Sarcomas are malignancies that arise from transformed cells of mesenchymal origin. Current classification schemes attempt to group sarcomas into subtypes that are useful for determining prognosis and formulating treatment strategies. In general, these neoplasms are grouped by mesenchymal cell of origin, head and neck sub site and histologic grade. The vast majority of tumors, approximately 80%, are of soft-tissue origin while the remaining 20% are of bony or cartilaginous origin [2]. Due to the multitude of tissue types, sarcomas are a heterogenous group of malignancies whose histologic characteristics reflect their tissue of origin. Histologic grade is a consistent predictor of prognosis and its importance is illustrated in the AJCC staging system for sarcomas [3]. Difficulty can arise in formulating a standardized treatment algorithm for sarcomas, as there are often inconsistencies in pathologic evaluations both from a histologic and grading standpoint. This inconsistency often makes it difficult to pool multi-institutional studies.

Here, we profile the clinical presentation, subtype distribution, and treatment results of 186 patients with sarcomas of the head and neck at a single tertiary academic center. The resulting group of patients was analyzed by multivariate analysis to define specific prognostic features that predict outcome and guide treatment approaches. Furthermore, careful subgroup analyses were performed to identify trends and sarcoma subtypes of distinct biologic behavior.

Methods

Patient Data

The study was approved by the University of California, Los Angeles Office of Protection of Research Subjections (institutional review board). Patients with head and neck sarcomas were identified from the pathology specimens received between 2000 and 2011 at the UCLA Ronald Reagan Medical Center through a computer-assisted search by the UCLA Tumor Registry in the Department of Pathology. 186 patients were identified and their clinical records were accessed for chart review.

Pathologic Review

All pathologic diagnoses were determined by Head and Neck pathologists at UCLA. Tumor histopathology including subtype, grade, margin status, perineural invasion, and lymph node

status were obtained. Tumors were classified as low-, intermediate- and high-grade. Tumor size was grouped by those with diameter greater than 5cm and those less than or equal to 5cm. Regional selective-lymph node dissection was performed in 39 patients and was designated as positive if one or more lymph nodes had evidence of regional spread. Patients who did not receive a neck dissection due to lack of clinical evidence based on physical exam and imaging were considered free of lymph node disease. Margins were classified as positive if tissue within 5mm of the margin was positive.

Statistical analysis

Primary outcomes included recurrence-free survival (RFS) and overall survival (OS). RFS was defined as the time from initial treatment to diagnosis of a local, regional, or distant recurrence. OS was defined as time to death from any cause. Kaplan Meier curves were constructed to visualize OS and RFS rates between groups. The differences were formally tested for using the log-rank test. Covariates were assessed for predictive performance with univariate and multivariate Cox proportional hazards regression models with regard to RFS and OS. Comparisons between groups were deemed statistically significant at the $p < 0.05$ threshold. Covariates were chosen for multivariate analysis based on factors identified as significant on univariate analysis (log rank $p < 0.05$). This method was chosen to minimize the total number of covariates thus improving the generalizability of the findings and minimizing instability in the model. As a default, age and gender were included in all multivariate models. Using this methodology, there were approximately 10 events per covariate for each model. Statistical analyses were performed in SPSS 21 (IBM Corp., Armonk, NY).

Results

Patient demographics

The mean age of the study population was 49 +/− 22 years. 58% of the patients were male and 42% were female (Table 1). Mean duration of follow-up for the entire group was 31 months. There was no follow up available in 12.9% of patients.

Clinical Presentation

Tumors most frequently presented as mass lesions (60%) and the nasal cavity/sinuses were the most common site (20.4%) followed by the neck (14%) and scalp (12.4%). Tumor size was greater than 5 cm in 47.3%, less than or equal to 5 cm in 26.3% and not reported in 26.3%. (Table 1)

Pathologic review

Solitary fibrous tumor/ hemangiopericytoma (SFT-HPC) was the most common subtype (22%) followed by osteosarcoma (13.4%), rhabdomyosarcoma (RMS) (10.2%), and angiosarcoma (9.7%)(Table 2). Tumors were high-grade in 35.5%, intermediate-grade in 14.5%, low-grade in 23.6%, and not reported in 26.4%. Lymph node metastasis was positive in 6.5% and was not performed in 79.1%. Perineural invasion was present in 6.5%, absent in 81.1% and not reported in 12.4%. Margins were positive in 35.5%, negative in 33.9%, and not reported in 30.6% (Table 1).

Treatment

In reviewing treatment modalities, the majority of patients (65.3%) received combination therapy. Surgery alone was performed in 29.3%, surgery with postoperative radiation therapy in 25.2%, and surgery with postoperative radiation therapy and chemotherapy in 24.0%. Nonsurgical treatment modalities included radiation alone in 0.54%, chemo alone in 4.3% and combination chemoradiation in 8%. (Table 1)

Recurrence-free survival and overall survival

Local recurrence occurred in 22.6%. Distant metastasis occurred in 19.9% of patients with the lung being the most common site (51.4%), followed by bone (27%) and liver (24.3%). 5-year OS and RFS was 49% and 50% among all subtypes (Figure 1). Angiosarcoma had the worst outcome with 2-yr RFS and OS of 34% and 22% respectively (Table 2).

Factors affecting recurrence-free and true survival

Patient and tumor factors were evaluated with respect to RFS and OS by univariate analysis (Table 3). Analysis revealed that grade (Log rank p = 0.009), margin status (Log rank p = 0.004), and perineural invasion (Log rank p = 0.023) all affected RFS. Grade (Log rank p = 0.001) and lymph node status (Log rank p = 0.001) both affected OS. Multivariate analysis based on the four factors significant by univariate analysis and including age and gender, showed that grade (p = 0.004) and margin status (p = 0.002) significantly impacted RFS and grade (p = 0.002) and age (p = 0.001) affected OS (Table 4).

Subtype Analysis

Table 3 displays univariate analysis for the eight most common sarcoma types in our series as well as five factors that were assessed for each tumor type. Subtype analysis revealed that margin status was a predictor of RFS for chondrosarcoma (Log rank p = 0.006). Size, perineural invasion and positive node status (Log rank p = 0.04, 0.029, and 0.002, respectively) significantly affected RFS for malignant peripheral nerve sheath tumor (MPNST). Analysis of OS showed that perineural invasion and positive lymph node status (Log rank p = 0.012 and 0.019, respectively) were significant predictors for RMS, grade (log rank p= 0.001) for chondrosarcoma, and positive lymph node status (log rank p = 0.002) for MPNST.

Discussion

Sarcomas of the head and neck are very rare accounting for approximately 1% of all head and neck neoplasms [4]. Due to this rarity, current treatment regimens rely on retrospective analyses of tertiary care institutions. Herein, we review the current literature and expand on the available data by reviewing 186 patient cases at our tertiary care institution. We further characterize the subtype distribution and treatment outcomes of head and neck sarcomas in order to further delineate the importance of certain variables in each specific disease entity. Adequate follow up and sample size allowed for univariate and multivariate survival analysis to identify prognostic factors affecting survival and recurrence.

Predictors of outcome

Prior studies on head and neck sarcomas have consistently shown grade, size, and margin status as prognostic indicators of recurrence and survival [5]. Few studies have been able to gain sufficient power to allow for multivariate analyses. Bentz et al. studied a series of 110 patients with head and neck sarcomas and evaluated fifteen patient and tumor characteristics. Multvariate analysis revealed that size, grade, and margin status affected relapse-free survival. Size and grade were also found to affect disease-specific survival and overall survival [5]. Indeed, our study corroborated some of these findings showing that margin status affects RFS ($p= 0.001$) and that grade affects RFS and OS ($p = 0.003$ and 0.001, respectively) on multivariate analysis. Interestingly, size was not a predictor of survival or recurrence in our study for sarcomas as a group (log rank $p = 0.87$ and 0.627, respectively.) As expected, age was identified as a factor predicting overall survival as all cause survival was reported.

Herein we also investigated lymph node status and perineural invasion as possible predictors of survival and recurrence. Univariate analysis demonstrated that the presence of perineural invasion affected RFS (log rank $p = 0.023$) and positive lymph node status affected OS (log rank $p = 0.001$). This is the first Head and Neck sarcoma study that has shown the presence of perineural invasion as a predictor of recurrence on univariate analysis.

Subtype analysis

Sarcomas of the head and neck are a varied group with multiple subtypes of distinct biological behaviors. As such, prognostic factors derived from grouped sarcoma data are difficult to apply to a specific sarcoma subtype. Few studies have attempted to look at subtype-specific factors. Although it is acknowledged that univariate analyses are limited in their interpretation, it is anticipated that these findings can guide future investigation.

Chondrosarcoma

On univariate analysis, margin status was shown to be a significant predictor of RFS (Log rank $p = 0.006$) and grade a significant predictor of OS (log rank $p = 0.001$) for chondrosarcoma. This is in agreement with the current literature on chondrosarcoma of the head and neck, which emphasizes the importance of negative margins and grade on survival and treatment outcomes [6].

Rhabdomyosarcoma

The mean age of patients with RMS was 21.7 consistent with the higher proportion of pediatric patients within this population. Subtype analysis revealed positive lymph node status (log rank $p = 0.019$) and the presence of the perineural invasion (log rank $p = 0.012$) as predictors of OS. The propensity for cervical metastasis is a known feature of RMS consistently shown in the literature and is a well-known predictor of outcome [7]. Other predictors of survival delineated in the pediatric literature include subtype (embryonal, alveolar, botryoidal, or pleomorphic), head and neck sub site (orbital, parameningeal, or nonparameningeal), distant metastases, extent, and residual disease after surgical resection [8]. Herein we show for the first time that perineural invasion as a predictor of survival in patients with RMS. Larger sample size will be needed to ascertain whether perineural

invasion is an independent predictor of survival or whether it is a surrogate marker of grade and/or subtype.

Malignant peripheral nerve sheath tumor

MPNST is an exceedingly rare tumor with an incidence of 0.1/100,000 of which only 10–15% present in the head and neck [9]. Understandably, there is very little data investigating predictors of outcome specific to the head and neck. Anghilieri et al. performed one of the largest studies to investigate predictors of survival in MPNSTs in their series of 205 patients. This study included head and neck, trunk, and extremity MPNSTs. Recurrent disease, tumor size, and site of origin were identified as the most important prognosticators for cause-specific survival. MPNST of the head and neck had the worst outcome [9]. Other smaller series have also shown that size, site, grade and Neurofibromatosis type 1 status as predictors of outcome [10–16]. In this study, tumor size, the presence of perineural invasion and positive lymph node status were identified to be predictors of RFS on univariate analysis (log rank $p = 0.04$, 0.029, and 0.002, respectively). Lymph node status was also found to be a predictor of OS (log rank $p = 0.002$). Herein, we offer the first report of predictors of survival and recurrence in head and neck MPNSTs.

Conclusion

There is a paucity of large series investigating head and neck sarcomas and further accounts are needed to substantiate past findings and add to the existing literature. We report that head and neck sarcomas tend to be high grade with a high incidence of positive margins. Grade and margin status were found to be the most important predictors of survival.

Subtype analysis revealed the first account of perineural invasion as a predictor of overall survival in patients in RMS. Additionally, this is the first study to show positive lymph node status and perineural invasion as predictors of survival in patients with head and neck MPNSTs.

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References

1. Potter BO, Sturgis EM. Sarcomas of the head and neck. Surg Oncol Clin N Am. 2003; 12:379–417. [PubMed: 12916461]
2. Sturgis EM, Potter BO. Sarcomas of the head and neck region. Curr Opin Oncol. 2003; 15:239–252. [PubMed: 12778019]
3. Van Damme JP, Schmitz S, Machiels JP, et al. Prognostic factors and assessment of staging systems for head and neck soft tissue sarcomas in adults. Eur J Surg Oncol. 2010; 36:684–690. [PubMed: 20542404]
4. Patel SG, Shaha AR, Shah JP. Soft tissue sarcomas of the head and neck: an update. Am J Otolaryngol. 2001; 22:2–18. [PubMed: 11172210]
5. Bentz BG, Singh B, Woodruff J, et al. Head and neck soft tissue sarcomas: a multivariate analysis of outcomes. Ann Surg Oncol. 2004; 11:619–628. [PubMed: 15172935]

6. Khan MN, Husain Q, Kanumuri VV, et al. Management of sinonasal chondrosarcoma: a systematic review of 161 patients. Int Forum Allergy Rhinol. 2013
7. Raney RB, Anderson JR, Barr FG, et al. Rhabdomyosarcoma and undifferentiated sarcoma in the first two decades of life: a selective review of intergroup rhabdomyosarcoma study group experience and rationale for Intergroup Rhabdomyosarcoma Study V. J Pediatr Hematol Oncol. 2001; 23:215–220. [PubMed: 11846299]
8. Dagher R, Helman L. Rhabdomyosarcoma: an overview. Oncologist. 1999; 4:34–44. [PubMed: 10337369]
9. Anghileri M, Miceli R, Fiore M, et al. Malignant peripheral nerve sheath tumors: prognostic factors and survival in a series of patients treated at a single institution. Cancer. 2006; 107:1065–1074. [PubMed: 16881077]
10. Cashen DV, Parisien RC, Raskin K, et al. Survival data for patients with malignant schwannoma. Clin Orthop Relat Res. 2004:69–73. [PubMed: 15346054]
11. Doorn PF, Molenaar WM, Buter J, et al. Malignant peripheral nerve sheath tumors in patients with and without neurofibromatosis. Eur J Surg Oncol. 1995; 21:78–82. [PubMed: 7851559]
12. Ducatman BS, Scheithauer BW, Piepgras DG, et al. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. Cancer. 1986; 57:2006–2021. [PubMed: 3082508]
13. Hruban RH, Shiu MH, Senie RT, et al. Malignant peripheral nerve sheath tumors of the buttock and lower extremity. A study of 43 cases. Cancer. 1990; 66:1253–1265. [PubMed: 2119249]
14. Sordillo PP, Helson L, Hajdu SI, et al. Malignant schwannoma--clinical characteristics, survival, and response to therapy. Cancer. 1981; 47:2503–2509. [PubMed: 6791802]
15. Wanebo JE, Malik JM, VandenBerg SR, et al. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 28 cases. Cancer. 1993; 71:1247–1253. [PubMed: 8435801]
16. Wong WW, Hirose T, Scheithauer BW, et al. Malignant peripheral nerve sheath tumor: analysis of treatment outcome. Int J Radiat Oncol Biol Phys. 1998; 42:351–360. [PubMed: 9788415]

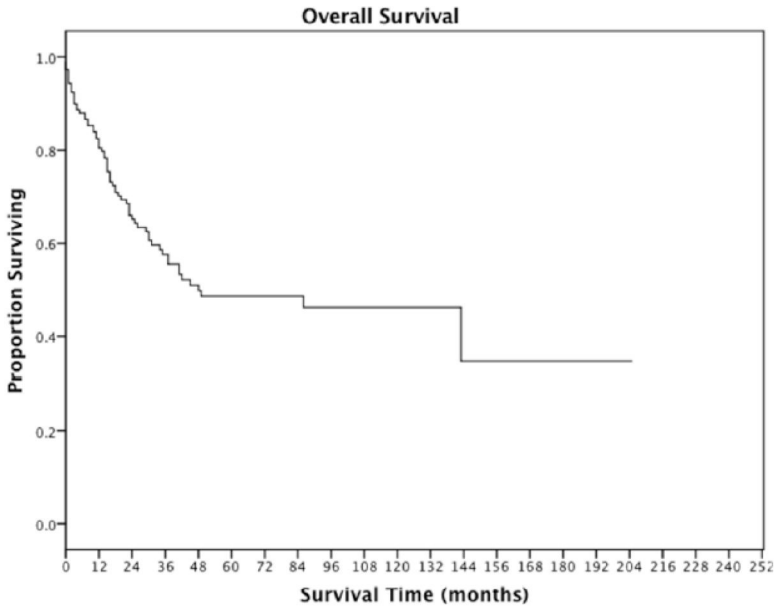

Fig. 1A

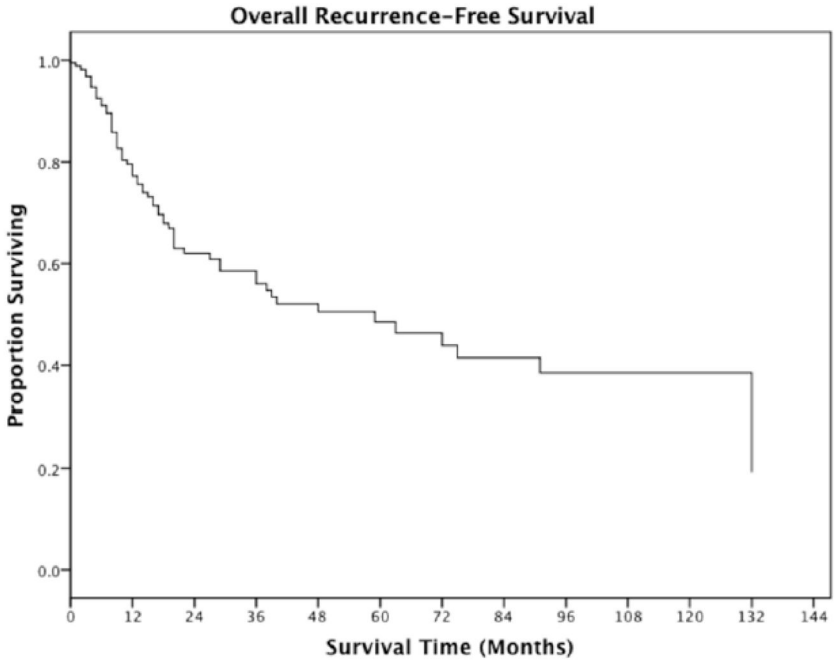

Fig. 1B

Figure 1.
Kaplan-Meier survival curves of recurrence-free survival (a) and overall survival (b) for all head and neck sarcomas.

Table 1

Patient demographics, tumor characteristics and treatment modality.

Characteristic	Frequency (%)
Sex	
Female	78 (42)
Male	108 (58)
Smoking history	38 (20)
Radiation history	28 (15)
Head and neck subsite	
Nasal cavity/sinuses	41 (22)
Neck	26 (14)
Orbit	24 (12.9)
Scalp	23 (12.4)
Face	20 (10.8)
Maxilla	15 (8.1)
Mandible	13 (7.0)
Base of skull	11 (5.9)
Larynx/pharynx	10 (5.4)
Other	9 (4.8)
Other skull bones	5 (2.7)
Oral cavity	4 (2.2)
Presenting symptoms at diagnosis	
Mass/lesion	112 (59.9)
Nasal obstruction	21 (11.2)
Numbness	15 (8)
Vision change	15 (8)
Headache	15 (8)
Pain	14 (7.5)
Epistaxis	10 (5.4)
Voice change	6 (3.2)
Dysphagia	3 (1.6)
Hearing loss/tinnitus	2 (1.1)
Othera	16 (8.6)
Grade	
Low	44 (23.7)
Intermediate	27 (14.5)
High	66 (35.5)
Not reported	49 (26.3)
Margin status	
Negative	71 (38.2)
Positive or less than 5mm from margin	58 (31.2)
Not reported	57 (30.6)

Characteristic	Frequency (%)
Max diameter	
Less than or equal to 5cm	88 (47.3)
Greater than 5cm	49 (26.3)
Not reported	49 (26.3)
Perineural invasion	
No	151 (81.2)
Yes	12 (6.5)
Not reported	23 (12.4)
Lymph node status	
Negative	174 (93.5)
Positive	12 (6.5)
Treatment modality	
Surgery alone	49 (26.3)
Surgery + radiation	42 (22.6)
Surgery + chemotherapy	12 (6.5)
Surgery + radiation + chemotherapy	40 (21.5)
Chemotherapy	8 (4.3)
Chemotherapy + radiation	15 (8.1)
Unknown	19 (10.2)

Table 2

Overall survival (OS) and recurrence-free survival (RFS).

Sarcoma Subtype	n (%)	Mean age (sd)	2-yr RFS	5-yr RFS	2-yr OS	5-yr OS
SFT-HPC	41 (22)	55.6 (18)	97%	67%	86%	49%
Osteosarcoma	25 (13.4)	39.5 (14.9)	49%	39%	68%	51%
RMS	19 (10.2)	21.7 (20.3)	64%	64%	83%	67%
Angiosarcoma	18 (9.67)	70.7 (9.8)	34%	-	22%	-
Chondrosarcoma	16 (8.6)	46.8 (17)	85%	74%	93%	71%
MPNST	13 (7)	41.5 (17)	62%	31%	58%	58%
Sarcoma NOS	13 (7)	59.1 (29.9)	44%	44%	34%	26%
Leiomyosarcoma	12 (6.45)	59.3 (14.1)	80%	32%	65%	55%
Liposarcoma	6 (3.2)	58.5 (12.2)	100%	100%	100%	100%
Pleomorphic	5 (2.7)	78 (17.5)	20%	-	33%	-
Synovial	5 (2.7)	38.8 (11.8)	50%	-	60%	-
Ewing’s	4 (2.2)	42.3 (13.5)	33%	33%	75%	25%
Myxofibrosarcoma	3 (1.6)	44.3 (29.9)	67%	67%	100%	100%
Kaposi’s	2 (1.1)	51.5 (16.2)	-	-	-	-
AFX	1 (0.5)	79	-	-	-	-
DFSP	1 (0.5)	28	-	-	-	-
Myofibroblastic	1 (0.5)	70	-	-	-	-
Giant cell	1 (0.5)	35	-	-	-	-
OVERALL	186	49.8 (22.1)	64%	50%	67%	49%

AFX = atypical fibroxantoma; DFSP = dermatofibrosarcoma protuberans; MPNST = malignant peripheral nerve sheath tumor; NOS = not otherwise specified; RMS = rhabdomyosarcoma; SFT-HPC = solitary fibrous tumor/hemangiopericytoma

Table 3

Univariate analysis of factors predicting recurrence-free and overall survival.

		Recurrence-Free Survival (log rank P-value)					Overall Survival (log rank P-value)				
Subtype	**N**	**Margin**	**Size**	**PNI**	**LN**	**Grade**	**Margin**	**Size**	**PNI**	**LN**	**Grade**
SFT-HPC	41	0.505	0.613	-	0.831	0.31	0.116	0.108	-	0.758	0.937
Osteosarcoma	25	0.131	0.401	0.948	0.202	0.341	0.639	0.913	0.826	0.127	0.694
RMS	19	1	0.919	0.307	0.235	-	0.157	0.639	0.012*	0.019*	-
Angiosarcoma	18	0.11	0.758	0.643	0.207	0.415	0.101	0.814	0.577	0.704	0.751
Chondrosarcoma	16	0.006*	0.478	-	-	0.506	0.109	0.478	-	-	0.001*
MPNST	13	0.376	0.04*	0.029*	0.002*	0.497	0.376	0.072	0.497	0.002*	0.321
Sarcoma NOS	13	0.429	0.715	0.801	-	0.329	0.487	0.515	0.857	-	0.16
Leiomyosarcoma	12	-		0.644	0.319	0.403	0.128	0.695	0.434	0.434	0.671
OVERALL	186	0.004*	0.627	0.023*	0.073	0.009*	0.909	0.87	0.195	0.001*	0.001*
Grade	N	Margin	Size	PNI	LN		Margin	Size	PNI	LN	
Low	44	0.017*	0.791	-	-		0.126	0.523	0.817	-	
Intermediate	27	0.014*	0.347	0.845	0.517		0.375	0.441	-	0.747	
High	66	0.241	0.82	0.86	0.601		0.424	0.548	0.321	0.065	

LN = lymph node status; PNI = perineural invasion.

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Table 4

Multivariate Cox-regression analysis of factors affecting recurrence-free and overall survival.

Factor	Recurrence-free survival	Overall survival
Age	1.013 (0.993–1.034), p = 0.193	1.028 (1.012–1.044), p = 0.001
Gender	0.947 (0.458–1.961), p = 0.884	0.699 (0.395–1.235), p = 0.217
Grade	2.013 (1.248–3.248), p = 0.004	1.976 (1.298–3.010), p = 0.002
Margin status	3.006 (1.500–6.024), p = 0.002	-
Perineural invasion	1.458 (0.459–4.629), p = 0.522	-
Lymph node status	-	1.197 (0.766–1.870), p = 0.430