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The impact of surgical resection margins on outcomes for adults with head and neck osteosarcomas: A Canadian sarcoma research and Clinical Collaboration (CanSaRCC) study

Sharon Tzelnick [a], Hagit Peretz Soroka [d,f], Najifah Tasnim [f], Ralph W. Gilbert [a], Jonathan C. Irish [a,g], David P. Goldstein [a], Dale Brown [a], Patrick Gullane [a], Douglas B. Chepeha [a], Christopher M.K.L. Yao [a], Axel Sahovaler [a], Ian J. Witterick [h], Eric Monteiro [h], Joel Davies [h], Shao Hui Huang [c], Brian O'Sullivan [c], Ezra Hahn [c], Ali Hosni [c], Albiruni Abdul Razak [d,e], Abha A. Gupta [b,d,f], John R. de Almeida [a,g,*]

[a] Department of Otolaryngology-Head and Neck Surgery/Surgical Oncology, Princess Margaret Hospital, University of Toronto, Ontario, Canada
[b] Division of Hematology/Oncology, Hospital for Sick Children, University of Toronto, Ontario, Canada
[c] Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, Ontario, Canada
[d] Department of Medical Oncology, Princess Margaret Cancer Centre, University of Toronto, Ontario, Canada
[e] Department of Medical Oncology, Mount Sinai Hospital, University of Toronto, Ontario, Canada
[f] CanSaRCC, Princess Margaret Cancer Center, Ontario, Canada
[g] Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada
[h] Department of Otolaryngology-Head and Neck Surgery, Mt Sinai Hospital, Toronto, Ontario, Canada

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ABSTRACT

Objective: The aim of the study is to describe the factors that influence outcome in adults with head and neck osteosarcoma (HNO) with a specific focus on the margin status.

Methods: Patients with a diagnosis of HNO between the years 1996–2021 were reviewed from the Canadian Sarcoma Research and Clinical Collaboration (CanSaRCC) Database. Baseline characteristics, pathology, treatment, and outcomes were analyzed. Univariable (UVA) and multivariable (MVA) Cox regression models were performed. 5-year locoregional control rate and overall survival (OS) were estimated using Kaplan-Meier method and Log-Rank test.

Results: Of 50 patients with a median age of 40 years (range 16–80), 27 (54%) were male. HNO commonly involved the mandible (n = 21, 42%) followed by maxilla (n = 15, 30%). Thirteen (33.3%) had low-intermediate grade and 26 (66.6%) had high grade tumors. Three patients (6%) had negative resection margins (>5 mm), 24 (48%) had close margins (1–5 mm), 15 (30%) had positive margins (<1mm) and 7 (16%) had unknown margin status. In total, 39 (78%) received chemotherapy – 22 (44%) received neoadjuvant chemotherapy while 17 (34%) received adjuvant chemotherapy. A total of 12 (24%) patients received radiotherapy, of whom 8 (16%) had adjuvant and 3 (6%) had neo-adjuvant. Median follow-up time was 6.3 years (range 0.26–24.9). Disease recurred in 21 patients (42%), of whom 15 (30%) had local recurrence only, 4 (8%) had distant metastasis, and 2 (4%) had both local and distant recurrence. 5-year locoregional control rate and OS was 62% and 79.2% respectively. Resection margins <3 mm was associated with lower 5 years OS and locoregional control rate (Log-Rank p = 0.02, p = 0.01 respectively).

Conclusion: Osteosarcomas of the head and neck are rare and local recurrence remains a concern. Surgical resection with negative resection margins may improve survival, and a 3 mm resection margin threshold may optimize survival. Radiotherapy and/or chemotherapy should be considered in a multidisciplinary setting based on risk-features.

* Corresponding author at: University of Toronto, Department of Otolaryngology-Head and Neck Surgery, Toronto General Hospital, University Health Network, 200 Elizabeth St, Toronto, ON M5G 2M9, Canada.
E-mail address: john.dealmeida@uhn.ca (J.R. de Almeida).

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Background

Osteosarcoma is an aggressive bone malignancy characterized by the formation of osteoid by malignant osteoblasts [1]. Head and neck osteosarcomas (HNO) are relatively rare accounting for 10% or fewer of all osteosarcomas and <1% of all head and neck cancers. HNO has an incidence of approximately 2–3 per 1 million persons per year [2–5]. The current treatment paradigm for high grade, resectable extremity osteosarcomas is neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy due to the high risk of occult metastases at first diagnosis, primarily in the lungs [6,7]. However, HNO differs from osteosarcoma of the extremities in that it presents at least two decades later compared to patients with extremity osteosarcomas [8], and are associated with relatively a lower rate of distant metastases [9,10]. Neoadjuvant chemotherapy has been associated with improved local control [11], and survival [12], while adjuvant radiotherapy has been associated with improved local control [12].

Oncologic resection of the craniofacial skeleton poses a surgical challenge. Firstly, achieving wide resection margins in the head and neck can be difficult, due to tumor proximity of vital structures such as the orbit and brain. Secondly, the use of intra-operative frozen section to assist surgeons with determination of completeness of resection is limited given the need to decalcify bone to determine the presence of disease. These challenges may explain the higher local recurrence rates (17–70%) in HNO compared to extremity osteosarcoma patients (5–7%) [13,14]. Positive resection margins have been strongly associated with a poor prognosis [15–17], however, the optimal cutoff between invasive tumor and resection margin in patients with the HNO has not been assessed previously [18]. Studies that examined the role of adjuvant radiotherapy for head and neck osteosarcoma has showed a survival advantage, mainly for patients with high risk features such as positive or close resection margins [17,19].

As a rare head and neck cancer entity, literature regarding HNO is scarce. Definitive treatment guidelines and protocols are lacking and are based mainly on extremity osteosarcoma. The aim of the study is to investigate features that may influence outcomes with a focus on margin size and role of additional therapies.

Methods

Study population and clinical information

After research ethics board approval, patient data was collated into the national prospective CanSaRCC database under defined consortium agreement. Data from patients with a diagnosis of HNO between the years 1996–2021 from two referral adult centers in Toronto (Princess Margaret Cancer Center and Mount Sinai Hospital) were extracted from the CanSaRCC (Canadian Sarcoma Research and Clinical Collaboration) Database.

Baseline sociodemographic and clinical data were obtained. The Charlson Comorbidity Index (CCI) was calculated from the medical charts. Resection margin status, R classification (R0, R1, R2), and distance from tumor and nearest resection margin in mm were ascertained from pathology reports.

The R classification defines an R0 resection as a complete resection without malignant cells at the borders of the resection, an R1 resection is defined as microscopic tumor cells present at the inked border of the specimen, and R2 resection refers to a resection with gross residual disease [20].

Treatment and follow up

All patients were seen by a multidisciplinary team where surgeons, radiation oncologists and medical oncologists assess the patients and make treatment decisions jointly. Surgery with adequate margins is the principal therapeutic modality for resectable non-metastatic HNO. Chemotherapy is discussed in multi-disciplinary tumour boards and is offered to patients with high grade disease, however, there is no institutional protocol per se demanding the use of chemotherapy in HNO, especially in non-high-grade lesions. Moreover, chemotherapy may be offered pre- and/or post-operatively. Postoperative RT is considered for patients with positive or close resection margins where re-resection is not possible. Preoperative RT is also considered after multidisciplinary discussion when an R0 resection would require sacrifice of critical anatomic structures (e.g. ocular or neurological) and/or where restricting the RT volume and minimizing the RT dose is desirable. Patients are generally followed with chest imaging (CXR or CT chest) and cross-sectional imaging of primary site (MR or CT, surgeon preference) every 3 months for first 2 years from diagnosis, then every 6 months until 5 years, and annually thereafter.

Statistical analysis

Locoregional control rate was defined as time to disease recurrence or progression and excluded death. 5-year locoregional control rate and 5-year overall survival (OS) were estimated using Kaplan-Meier method and Log-Rank test. T-test, Anova and Wilcoxon rank were used to compare means and medians between groups. Chi-square and Fisher's test were used to compare demographic features. Univariable (UVA) and multivariable (MVA) Cox regression models were computed for variables associated with survival outcomes.

A threshold analysis was performed to determine the distance in mm that provided the best discrimination of survival above and below the cut-point using Kaplan-Meier methods for both OS and locoregional control rate.

All tests were two-sided with p value of <0.05 considered as statistical significance.

Results

Clinical and demographic data

The cohort included a total of 50 patients with median age of 40 years (range 16–80). Twenty-seven patients (54%) were male and the majority of patients (63.46%) had Charlson Comorbidity Index (CCI) of $\leq$2. Nine patients (18%) had a Radiation induced Sarcoma (RIS). RIS patients were significantly older than patients with primary HNO (mean age 52.8 vs. 38.7, p = 0.027). HNO most commonly involved the mandible (n = 21, 42%) followed by maxilla (n = 15, 30%). Clinical and demographic data are presented in Table 1.

Treatment

All patients had surgery, of whom 13 (33.3%) had low or intermediate grade and 26 (66.6%) had high grade tumors with a mean tumor size of 4.1 ($\pm$2.1). The majority of patients 74% (n = 37) had an R0 resection. Three patients (6%) had negative margins (>5mm), 24 (48%) had close margins (between 1 and 5 mm), 15 (30%) had positive margins (<1mm) and 8 (16%) patients had unknown margin status. 18 (36%) patients underwent neck dissection: 14 had ipsilateral dissection and 4 patients had bilateral neck dissection. Only one patient had positive nodal disease. A total of 39 (78%) patients received chemotherapy: 22 (44%) received neoadjuvant chemotherapy while 17 (34%) received adjuvant chemotherapy. A total of 12 (24%) patients received radiotherapy, of whom 8 (16%) had adjuvant and 3 (6%) had neo-adjuvant radiation therapy. Of the 8 patients who received adjuvant radiotherapy, 5 had positive resection margins (<1mm), 2 patients had close resection margins (both with the closest margin being 2 mm) and one patient had unknown margin status.

Table 1
Demographic and clinical charectaristics of 50 Patients With OS.

		N (%)
SEX	Male	27 (54)
	Female	23 (46)
AGE AT DIAGNOSIS (Years)	Median	40
	Range	(16–80)
CHARLSON COMORBIDITIES INDEX	≤2	35 (70)
	>2	15 (30)
MAX DIAMETER OF PRIMARY (cm)	Median	4.1
	Range	(1.2–9.3)
PATHOLOGY	Osteosarcoma (NOS)	24 (48)
	Epitheliod OS	1 (2)
	Chondroblastic OS	13 (26)
	Oteoblastic OS	6 (12)
	Giant cell rich OS	1 (2)
	Fibroblastic OS	3 (6)
	Periosteal OS	1 (2)
	Extraskeletal OS	1 (2)
RADIATION INDUCED SARCOMA	Yes	9 (18)
	No	41 (82)
SITE OF PRIMARY	Mandible	21 (42)
	Maxilla	15 (30)
	Skull base	5 (10)
	Extraskeletal	4 (8)
	Other	5 (10)
GRADE	Low-intermediate	13 (33.3)
	High	26 (66.7)
SURGERY	Yes -Free flap	30 (60)
	–No free flap	20 (40)
CLOSEST MARGINS	≤3	33 (66)
	>3	9 (18)
RADIATION	No	39 (78)
	Preop	3 (6)
	Postop	8 (16)
CHEMOTHERAPHY	No	11 (22)
	Neoadjuvant	22 (44)
	Adjuvant	17 (34)

Recurrence and survival analysis

The median follow-up for the entire cohort was 6.3 years (range 0.26–24.9). Disease recurrence was observed in 21 (42%) of patients, of whom 15 (30%) had local recurrence, 4 (8%) had distant metastasis, and 2 (4%) patients had both local and distant recurrence. No nodal/regional failures were reported. Five-year locoregional control rate and 5-year OS was 62% and 79.2% respectively. Survival analysis of patients with closest margins <3 mm showed lower 5 years OS and locoregional control rate compared to patients with closest margins above 3 mm (Log-Rank p = 0.02, p = 0.01 respectively) (Figs. 1 and 2). All patients with local recurrence had closest margins <3 mm; of them, a single patients had pre-operative radiotherapy and six patients received adjuvant radiotherapy. Residual tumor classification (R status) was not a prognostic factor for survival (p = 0.3, HR 1.3 CI 95% 0.75–2.47). In UVA, patients with radiation induced sarcoma (RIS) were associated with lower OS (p = 0.02, HR = 3.7, 95% CI 1.4–10.5). In addition, patients with high grade disease had a lower locoregional control rate (p = 0.04, HR = 4.73 CI 95%1.07–20.9). In UVA, the receipt of radiotherapy or chemotherapy did not influence locoregional control rate (p < 0.001, HR = 5.4 CI 95% 2.2–12.1; p = 0.73, HR = 0.85 CI 95% 0.33–2.17 respectively) or OS (p = 0.01, HR = 3.84 CI 95% 1.33–11.7; p = 0.18, HR = 0.66 CI 95% 0.37–4.69 respectively) although these analyses did not account for extent of disease and pathologic features. Table 2 presents patients outcomes.

Discussion

In this registry, two-institution study, we demonstrated overall survival rates of 80% in patients with HNO. The primary pattern of disease failure was local recurrences, and completeness of surgical resection impacted disease outcomes. Although a small cohort, a threshold of 3 mm from the tumor edge to the resection margin provided the optimal discrimination of survival, suggesting that previously established margin cut-points may need to be reconsidered. Distant failures were relatively rare in this cohort, although this may be due to the delivery of chemotherapy. Treatment of these rare tumors requires multidisciplinary discussion with medical oncologist and radiation oncologist and often requires multi-modal treatment for patients with high-risk features.

Treatment protocols for HNO have largely mirrored those of extremity osteosarcoma. Current treatment guidelines for extremity osteosarcoma are largely based on the Cooperative Osteosarcoma Study Group (COSS) protocols, which combine neoadjuvant chemotherapy, surgery and adjuvant chemotherapy. These protocols have been associated with improved overall survival (OS) compared to surgery alone (60%–80% vs 10%–20%) in patients with extremity osteosarcoma [21–23]. However, the benefits of these protocols in HNO have been difficult to establish due to a relative dearth of information. In some larger studies, Shim et al. [24] found no survival difference between patients treated with surgery and any combination of neoadjuvant chemotherapy, adjuvant chemotherapy, or radiotherapy in a retrospective study of 841 patients with HNO from the National Cancer Database (NCDB). Studies by Guadagnolo et al, Chen at al., and Smeele et al have shown similar results [8,17,25]. However, several smaller studies [2,26–30] have shown survival benefit with the addition of chemotherapy to surgery in the head and neck population. Although our study failed to demonstrated a clear benefit of these additional modalities, it is our institutional policy that all patients with HNO be evaluated by a multi-disciplinary team, and most patients (particularly those with high-grade tumors) are treated with neo-adjuvant chemotherapy, followed by surgical resection and adjuvant chemotherapy and/or radiotherapy depending on the presence of high-risk features such as positive resection margins.

Local recurrence in the HNO patients is not uncommon [14,31]. Previous studies have shown that positive resection margins are strongly associated with poor prognosis [15–17], however, little work has been done to identify the optimal resection margins. We aimed to explore the impact of margins on survival in the head and neck population. Various systems exist for the classification of surgical margins in sarcoma; however, the use of the American Joint Committee on Cancer (AJCC) residual tumor classification (R classification) is frequently used for reporting [32]. The AJCC manual classifies an R0 resection as a complete resection without malignant cells at the borders of the resection, an R1 resection is defined as microscopic tumor cells present at the inked border of the specimen, and R2 resection refers to a resection with gross residual disease. Several studies evaluating surgical margins in extremity soft tissue sarcoma have used this classification system and found that it is associated with local recurrence [33–35]. More recently, there increasing interest in exploring the definition of margins as the distance between normal tissue and tumor. Gundle et al. [36] studied 2217 patients with soft tissue sarcoma in the extremities, chest and abdominal wall, and paraspinal region. The results suggested that

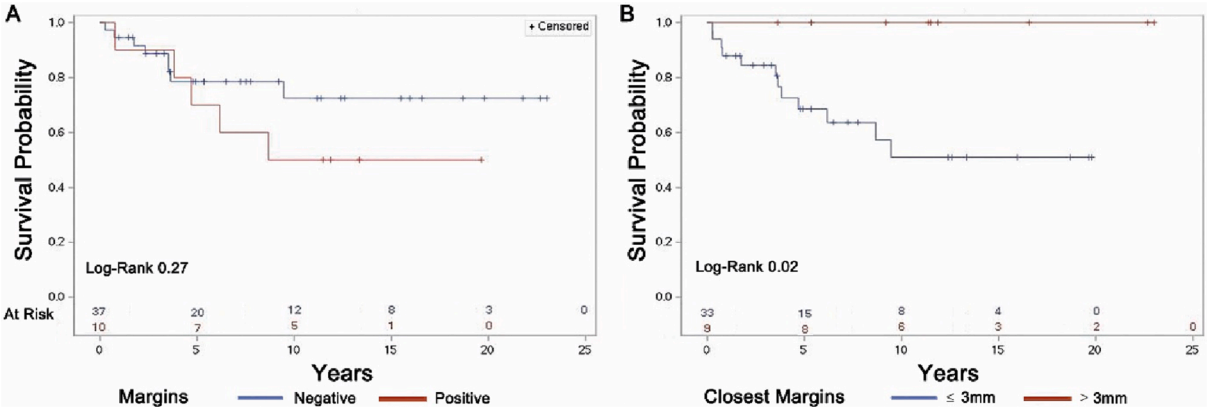

Figure 1. Kaplan-Meier plot for overall survival. (A) Kaplan-Meier plot with positive/ negative resection margins (B) Kaplan-Meier plot with resection margins of 3 mm.

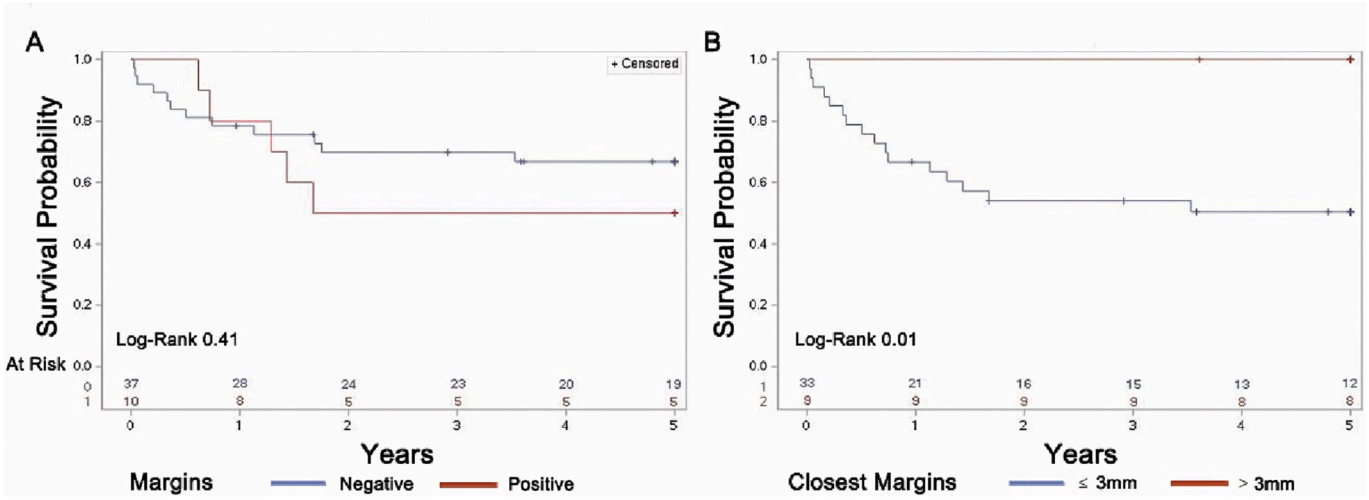

Figure 2. Kaplan-Meier plot for 5-years recurrence-free survival. (A) Kaplan-Meier plot with positive/ negative resection margins (B) Kaplan-Meier plot with resection margins of 3 mm.

Table 2
Patients outcome.

		Total N = 50	Closest margins ≤ 3 N = 33 (66%)	Closest margins ≤ 3 N = 9 (18%)	P Value
Status	Alive	35 (70%)	21	9	0.03
	Deceased	15 (30%)	12		n/a
RIS	No	41 (82%)	24	9	0.009
	Yes	9 (18%)	9		n/a
Recurrence	No	29 (58%)	16	9	0.16
	Yes	21 (42%)	17		n/a
Status of recurrence	Local	15 (30%)	13		n/a
	Distant	4 (8%)	4		n/a
	Both	2 (4%)			n/a
Overall survival	Years, Median (Range), N (%)	6.33 (0.26–24.89), 50 (100%)	4.79 (0.26–19.80), 33 (66%)	11.48 (3.41–23.02), 9 (18%)	0.02

patients who had <1-mm margin of normal tissue between the inked specimen and tumor have a local recurrence rate lower than patients with R1 resections, and similar to patients with R0 resections. A recent review by the French sarcoma group (GROUPOS) and the bone tumor study group (GSF-GETO/RESOS) [37] evaluated the prognostic value of margins in bone sarcoma. In this study, >2 mm of distance from the tumor edge and resection margin was established as an optimal threshold for predicting local recurrence. Margin assessment is widely used in the surgical treatment of head and neck mucosal squamous cell carcinoma and achieving resection margins of >5 mm is believed to reduce the likelihood of local recurrence [38–41]. Studies that examined the optimal cutoff for margins report a linear relationship between increasing margin distance and improved outcomes [41–43]. We applied a similar framework to head and neck osteosarcoma. Stratifying patients into low and high-risk groups based on margin status is important for head and neck osteosarcoma because achieving wide resection margins is difficult in the head and neck given the proximity of several important anatomic structures. This study is the first to define a threshold of optimal surgical margins that corresponds with survival. We have shown that resection margins stratified by a cut-point of 3 mm

correlates is differentially prognostic, while R resection status was not in the present analysis.

Our study further evaluated the benefit of non-surgical treatments on oncologic outcomes. Although our analysis did not confirm a survival benefit of radiotherapy or chemotherapy in this disease population, this was likely due to a relatively small sample size and more intensive treatments offered to patients with high-risk disease. Interestingly, we observed a relatively low rate of distant metastatic disease in this cohort relatively to patients with extremity sarcoma. Whether this finding is due to the receipt of chemotherapy or due to a different biology of disease is difficult to answer in a small study. Regardless, our recommendation and institutional approach is for multi-disciplinary discussion and that treatments should be based on reducing the risk of disease recurrence based on extent of disease and pathologic features.

This study has several limitations. As this is a rare entity, our study has a small sample size. Moreover, given the extended time period of the study, some patients did not have reported margin status and it might be possible that outcomes in this groups were different than the ones analyzed with well-documented margin status. Lastly, our treatment regimens were not homogenous due to the retrospective nature of our study. A multi-center national database and international multi-disciplinary collaborations are needed to overcome these limitations.

Conclusion

Osteosarcoma is a rare head and neck cancer entity in which local recurrence remains a concern. Ideal outcomes are achieved in a multi-disciplinary setting. Surgical resection with negative margins of at least 3 mm optimize survival outcomes. Further validation in large multi-institutional studies are needed to confirm these findings.

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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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