

Pediatric Head and Neck Osteosarcoma Prognosis, Survival and Cancer-Susceptibility Gene Variants

Victor H Alborno Alvarez, BS¹; Daniel C Chelius, MD^{1,2}; Amy L Dimachkieh, MD^{1,2}

¹Baylor College of Medicine, Department of Otolaryngology-Head and Neck Surgery

²Texas Children’s Hospital, Pediatric Otolaryngology



Abstract

Importance: Pediatric head and neck osteosarcoma is rare, and the complex three-dimensional anatomy makes resection margins difficult to assess. Insight on this unique disease is warranted to improve the management.

Objective: To compare the 3- and 5-year overall survival (OS) and event-free survival (EFS) of osteosarcomas of the head and neck (OSTHN) in our institution to the European and American Osteosarcoma Study (EURAMOS-1), the largest cohort on osteosarcomas, and to evaluate the frequency of germline mutations in cancer-susceptibility genes.

Evidence Review: A retrospective analysis of patients with OSTHN at our institution from January 2012 to November 2020 was performed. A literature review was conducted.

Findings: A total of eight patients with OSTHN were identified with a mean age of 14 years. There were six male patients (75%). Head and neck locations were skull (75%) and maxilla (22%). Only three patients (38%) had primary OSTHN without a history of malignancy. The 1-, 3-, and 5-year OS from time of biopsy of the OSTHN were 88% (*n*=8), 67% (*n*=6), and 60% (*n*=5). The 3- and 5-year OS in the EURAMOS-1 cohort in all tumor subsites in individuals age < 40 years old, were 79% and 71%. The 1-, 3-, and 5-year EFS from surgical resection were 75% (*n*=8), 43% (*n*=7), and 43% (*n*=7). The 3- and 5-year EFS in the EURAMOS-1 cohort were 59% and 54%. Three individuals (38%) had germline mutations in cancer-susceptibility genes: TP53, RECQL4 helicase, and RB1.

Conclusions and Relevance: While the overall survival of our OSTHN cohort compares to the OS of all subsites in the EURAMOS-1 cohort, the EFS was lower. This study is limited by its small sample size, but there is a trend of high incidence of OSTHN as a second primary and decreased EFS compared to other anatomic subsites. At least 38% of the individuals in our cohort had an underlying cancer-susceptibility germline mutation, compared to 28% in other series. Head and neck osteosarcomas should be analyzed separately in future osteosarcoma collaborative studies.

Introduction

Osteosarcoma (OST) is the most common bone malignancy in children and young adults with an annual incidence of 2.8-3.8 individuals per million.¹ It arises sporadically or in the setting of previous local radiation exposure, genetic susceptibility, preexisting benign bone disease, or trauma.^{2,3} Key differences between limb and head and neck subsites are summarized in the table below:

	Limb	Head and neck
Population ¹	bimodal distribution with a major peak in adolescence and a minor peak in the elderly population	rarely seen in adolescence
Subsite distribution ¹	upper - 9% lower - 61%	mandible and maxilla - 9% skull and facial bones - 3%
Disease presentation ⁴	most frequently painful with or without swelling	most frequently swelling with or without pain
Local recurrence rate ^{4,5,6,7}	3 to 6%	37% in Guadagnolo et al
Distant metastasis rate ^{6,8,9}	39% at presentation and 61% throughout treatment course in Yasini et al	2% at presentation in Laskar et al and 21% throughout treatment course in Guadagnolo et al
TP53 pathogenic variant ⁵	Less likely	More likely

Among the most important OST studies to date are:

- EURAMOS-1, the largest cohort, in which all enrolled participants received standard of care therapy to determine survival and prognostic factors. Head and neck subsite was included in axial skeleton¹⁰
- Whole exome sequencing or targeted sequencing study to identify frequency of pathogenic variants³

Given the anatomical boundaries of osteosarcoma of the head and neck (OSTHN) and the rarity of this disease in the pediatric population, we describe our institutional experience of the clinical course, compare survival outcomes to those of EURAMOS-1, and determine the presence of cancer susceptibility genes in our cohort.

Methodology

A retrospective chart analysis of all patients treated for OSTHN at Texas Children’s Hospital (TCH) in Houston, TX, USA from January 2012 to November 2020 was performed after approval of the Baylor College of Medicine Institutional Review Board. All head and neck malignancies were independently confirmed by our institution’s Department of Pathology.

Primary outcomes were:

- 1-, 2-, 3-, and 5-year Event-Free Survival (EFS)
- Overall Survival (OS)

EFS was defined as time of initial diagnostic biopsy to time of first event (new or progressed metastasis, local recurrence or progression, or secondary malignancy). Overall-survival (OS) was determined from time of diagnosis to death or time of most recent follow-up. The frequency of germline mutations in cancer-susceptibility genes was also determined. A literature review was conducted for pediatric head and neck osteosarcoma and osteosarcoma genetics using a MEDLINE key term search.

Baseline characteristics were described using numbers and percentages for categorical variables. EFS and OS curves were estimated using the Kaplan-Meier method.¹¹

Results

A total of eight patients were identified. Clinical data of each patient is shown below:

Pt	Sex	Age	Hx of CA	FCS	Bone site	H	Presenting sx(s)	Greatest DIM (cm)	Tx (S, CT, RT)	Surgical margins (R0 or R1)	LR	Met	Time to first event (mo.)	Outcomes (mo.)
1	M	23	Y	RTS	L maxilla	fb	Pain, numbness, and eye tearing	4.8	S	R1	Y	N	19	NED 29
2	M	18	Y	RB1	L parietal bone	unk	Headache, swelling, warmth	1.8	S	R1	N	N	16	NED 16
3	M	11	Y	N	L clinoid process	unk	Blurry vision, headache, nosebleed	1.4	RT	NA	NA	Y	0	DOD 3
4	F	4	Y	N	Clivus and L occipital condyle	unk	Headache	unk	S + CT	R1	N	N	72	NED 72
5	M	13	Y	N	L parietal bone	ob	asx	1.6	S + CT	R0	Y	Y	9	DOD 19
6	M	13	N	N	L parietal and temporal bone	ob	Swelling	6	S + CT	R1	N	N	108	NED 108
7	M	14	N	N	Sinonasal cavity	cb	Swelling, epistaxis	7.5	CT + S + RT	R1	N	N	104	NED 104
8	F	13	N	LFS	R maxilla	cb	Pain, numbness, double vision	5.1	CT + S + CT	R0	Y	N	20	NED 47

Pt, patient; M, male; F, female; Hx, history; CA, cancer; Y, yes; N, no; FCS, familial cancer syndrome; RTS, Rothmund-Thomson syndrome; RB1, *de novo* RB1 mutation; LFS, Li-Fraumeni syndrome; L, left; R, right; H, histological type; fb, fibroblastic; ob, osteoblastic; cb, chondroblastic; met, metastatic; unk, unknown; sx(s), symptom(s); asx, asymptomatic; DIM, dimension; Tx, treatment; S, surgery; RT, radiotherapy; CT, chemotherapy; P, palliative therapy; R0, complete resection with negative surgical margins, R1, gross total resection with positive or uncertain surgical margins; NA, not applicable; LR, local recurrence; Met, metastasis; mo, months; F/U, follow-up; NED, no evidence of disease; DOD, died of disease.

Results (continued)

The following are our sample and tumor characteristics, respectively:

	Population Characteristics
Male to female ratio	3:1
Mean Age	14 years (range 4-23)
Mean follow-up from diagnosis (<i>n</i> =8)	4.1 years (range 0.3-9)
Mean follow-up from surgical resection (<i>n</i> =7)	4.6 years (range 1.3-9)
Familial Cancer Syndromes	Li-Fraumeni (<i>n</i> =1), Rothmund-Thomson (<i>n</i> =1), <i>de novo</i> RB1 mutation (<i>n</i> =1)
Previous malignancies	OST of the limb [tibia (<i>n</i> =3), femur (<i>n</i> =2), radius (<i>n</i> =1), fibula (<i>n</i> =1)], lung (<i>n</i> =1), retinoblastoma (<i>n</i> =1), posterior fossa (<i>n</i> =1)
Previous chemotherapies	ifosfamide (<i>n</i> =3), cisplatin (<i>n</i> =4), carboplatin (<i>n</i> =1), doxorubicin (<i>n</i> = 4)
Comorbidities	prior orthopedic surgery (<i>n</i> =4) and eye surgery (<i>n</i> =1), eustachian tube dysfunction (<i>n</i> =1), impairment in activities of daily living (<i>n</i> =1)

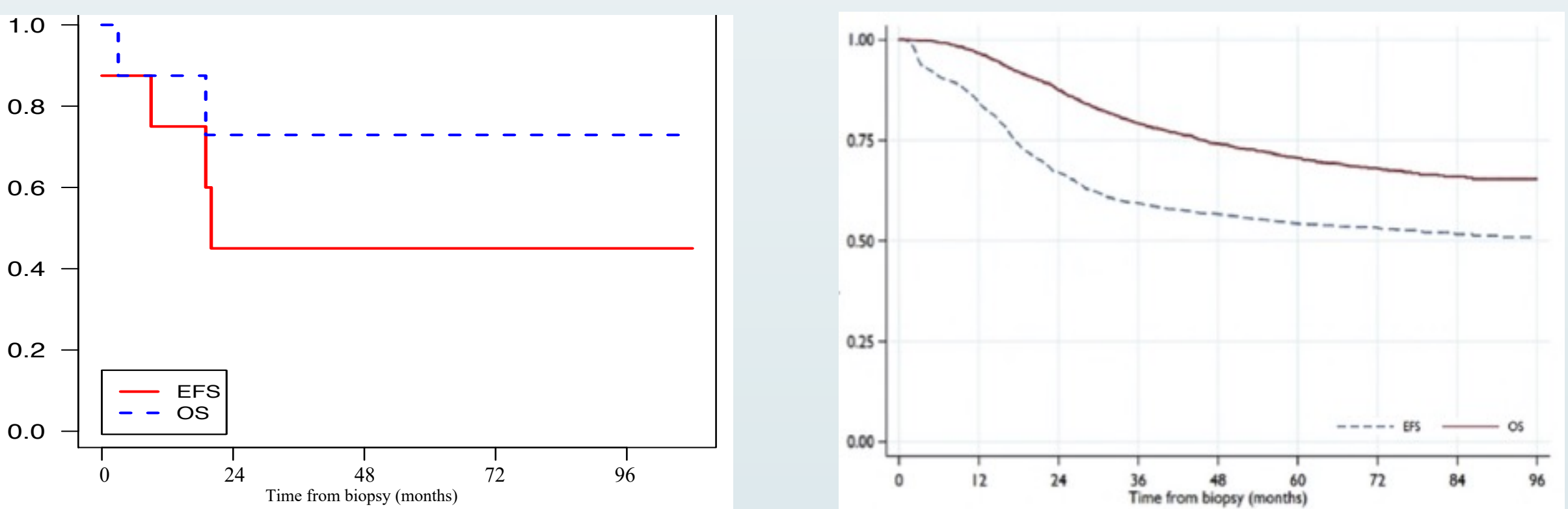
	Tumor Characteristics
Head and neck subsites	maxilla (<i>n</i> =2), skull (n=6) [parietal (<i>n</i> =2), parietal and temporal (<i>n</i> =1), occipital (<i>n</i> =1), sphenoid (<i>n</i> =1), and sinonasal (<i>n</i> =1)]
Mean greatest dimension at diagnosis	4 cm (<i>n</i> =7)
Histological types	osteoblastic (<i>n</i> =2), chondroblastic (<i>n</i> =2), fibroblastic (<i>n</i> =1)
Most common presenting symptoms including local recurrences	headache (<i>n</i> =4), pain (<i>n</i> =3), swelling (<i>n</i> =3), asymptomatic (<i>n</i> =3), numbness (<i>n</i> =2), epistaxis (<i>n</i> =2), vision loss (<i>n</i> =2)
Local recurrences	orbit (<i>n</i> =1), maxilla (<i>n</i> =1), orbit and maxilla (<i>n</i> =1), and parietal bone (<i>n</i> =1)
Metastases	tibia, femur, and lung on presentation (<i>n</i> =1), cervical spine and lung nine months post-operative (<i>n</i> =1)
Radiation-induced osteosarcomas ^{3,12}	two patients (33%) as per criteria defined by Cahan et al and Arlen et al
Margins	R0 (<i>n</i> =2, 25%), R1 (<i>n</i> =5, 63%).

Postoperative complications were vertebral artery pseudoaneurysm, hydrocephalus, and pseudomeningocele (*n*=1) and vision loss and darkening after orbit-sparing total maxillectomy (*n*=1).

The following table compares our institutional EFS and OS with those in EURAMOS-1:

	TCH study	EURAMOS-1 ¹⁰
EFS	1-year: 75% 3-year: 43% 5-year: 43%	3-year: 59% 5-year: 54%
OS	1-year: 88% 3-year: 67% 5-year: 60%	3-year: 79% 5-year: 71%

Kaplan Meier plots for EFS and OS in our study (left) and in EURAMOS-1¹⁰ (right) are shown below:



The following table compares our institutional frequency of pathogenic variants to the study by Mirabello et al:

	TCH institutional experience	Study by Mirabello et al ³
Presence of pathogenic variants	At least 38% (<i>n</i> =3)	28% (<i>n</i> =281)

Discussion

Our institutional 3- and 5-year EFS for pediatric OSTHN was 43% and 43%, compared to the EURAMOS-1 study, with a 3- and 5-year all subsites EFS of 59 and 54%, respectively and axial skeleton subsite HR of 1.53.¹⁰ The axial skeleton (including OSTHN) was found to be a significant independent predictor of poor outcomes.¹⁰

The majority of events in our cohort were local recurrence in 43% of all patients who underwent surgical resection. These findings reflect the challenge of axial skeleton surgery and not necessarily a more aggressive tumor biology as our results are similar to those with narrow (HR 1.11) or positive (HR 1.98) microscopic margins when controlling for histologic type and tumor volumes.¹⁰

Current treatment protocols for pediatric OSTHN are derived from large studies primarily consisting of adult patients or all pediatric anatomic subsites like EURAMOS-1. A limitation of the EURAMOS-1 study is the exclusion of patients with surgically unresectable disease, which was the case in one of our patients. It is possible that a higher population of OSTHN was excluded compared to osteosarcomas from other sites given the anatomical boundaries that make head and neck cancer resection challenging. The EURAMOS-1 study also excluded patients with a history of chemotherapy or other osteosarcomas, which is 63% of our patients. This makes it very challenging to apply the EURAMOS-1 data to the pediatric OSTHN population; however, these data drive the majority of the oncologic treatment algorithms for our patients.

Pediatric OSTHN is a special population because these malignancies are more common in adults. Caution must be employed when extrapolating information on prognosis and treatment in the pediatric setting. For example, although large OST studies including adults have reported 9% of tumors in the mandible and 3% of tumors in the skull and other flat bones of the head and neck, our cohort of pediatric OSTHN patients all had tumors of the skull and facial bones which are more complicated to address surgically than the mandible.¹ Since pathogenic variants may be more prevalent in children, it is also plausible that these tumors in children respond differently to treatment.

Conclusion

While the overall survival of our OSTHN cohort compared to the OS of all subsites in the EURAMOS-1 cohort, the EFS was lower. This study is limited by its small sample size, but there is a trend of high incidence of OSTHN as a second primary and decreased EFS compared to other anatomic subsites.

The oncologic guidelines that drive the treatment of pediatric OSTHN are developed from studies such as the EURAMOS-1 study, but pediatric OSTHN are distinct and more specific investigations and independent stratifications of the head and neck subsite are needed to investigate these patients further.

At least 38% of the individuals in our cohort had an underlying cancer-susceptibility germline mutation, compared to 28% in other series.

A clearly defined treatment guideline for pediatric OSTHN is warranted. Head and neck osteosarcomas should be analyzed separately in future osteosarcoma collaborative studies.

References

- Berner K, Johnsson TB, Berner A, et al. Time-trends on incidence and survival in a nationwide and unselected cohort of patients with skeletal osteosarcoma. *Acta Oncol*. 2015;54(1):25-33.
- Cahan W, Helen Woodard, Hingorham N, Stewart F, Coley B. Sarcoma arising in irradiated bone. 1948;1:3-29.
- Mirabello L, Zhu B, Koster R, et al. Frequency of Pathogenic Germline Variants in Cancer-Susceptibility Genes in Patients With Osteosarcoma. *JAMA Oncol*. 2020;6(5):724.
- Mandiger O, Givoli N, Talim YP, Taicher S. Osteosarcoma of the jaw: The Chaim Sheba Medical Center experience. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001;91(4):445-451.
- Mark RJ, Sencarz JA, Tran L, Dodd LG, Selch M, Calciatera TC. Osteogenic Sarcoma of the Head and Neck: The UCLA Experience. *Arch Otolaryngol Neck Surg*. 1991;117(7):761-766.
- Guadagnolo BA, Zagars GK, Raymond AK, Benjamin RS, Sturgis EM. Osteosarcoma of the jaw/craniofacial region. *Cancer*. 2009;115(14):3262-3270.
- Bacci G, Ferrari S, Mercuri M, et al. Predictive factors for local recurrence in osteosarcoma 540 patients with extremity tumors followed for minimum 2.5 years after neoadjuvant chemotherapy. *Acta orthopaedica*. 1998;69(3):230-236.
- Yasin NF, Abdul Rashid ML, Ajit Singh V. Survival analysis of osteosarcoma patients: A 15-year experience. *J Orthop Surg (Hong Kong)*. 2020;28(1):2309499019896662.
- Laskar S, Bano A, Muckadam MA, et al. Osteosarcoma of the head and neck region: Lessons learned from a single-institution experience of 50 patients. *Head Neck*. 2008;30(8):1020-1026.
- Smeland S, Bielack SS, Whelan J, et al. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. *Eur J Cancer*. 2019;109:36-50.
- Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *J Am Stat Assoc*. 1958;53(282):457-481.
- Arlen M, Hingorham N, Huvois A, Marcove R, Miller T, Shah JC. Radiation-induced sarcoma of bone. 1971;28(5):1087-1099.