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Research Article

Osteosarcoma of the Jaws in Adult Patients: A Clinic Opathological Study of 14 Patients

Ayse Durnali[1]*, Necati Alkis[1], Fisun Ardic Yukruk[2], Asiye Ugras Dikmen[3], Tulay Akman[4], Mehmet Metin Seker[5], Mevlude Inanc[6] and Berna Oksuzoglu[1]

[1]Department of Medical Oncology, Dr. A.Y. Ankara Oncology Training and Research Hospital, Turkey
[2]Department of Pathology, Dr. A.Y. Ankara Oncology Training and Research Hospital, Turkey
[3]Sincan Public Health Center, Turkey
[4]Department of Medical Oncology, Dokuz Eylul University Faculty of Medicine, Turkey
[5]Department of Medical Oncology, Cumhuriyet University Faculty of Medicine, Turkey
[6]Department of Medical Oncology, Erciyes University Faculty of Medicine, Turkey

***Corresponding author:** Ayşe Durnali, Department of Medical Oncology, Dr A.Y. Ankara Oncology Training and Research Hospital, Ankara, 13. Street No:56, TR- 06200, Yenimahalle, Ankara, Turkey, Tel: +90-312-3360909 Ext:5705; Fax: +90-312-3454979; Email: aysadurnali@gmail.com

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Abstract

Osteosarcoma of the jaw is a rare disease and there is limited knowledge about prognostic parameters and optimal treatment modality. We aimed to analyze outcomes and prognostic parameters of our patients. Clinicopathological records and treatment outcomes the 14 adult's patients with osteosarcoma of the jaws, identified and treated from August 1997 to August 2011, were analyzed retrospectively. Seven patients were male and 7 were female; median age was 27.5 (range: 17-52 years). Twelve patients (86%) had high grade tumor, most common histopathological type was chondroblastic (45%). No patient had distant metastasis at the time of diagnosis. Of the 12 patients (85.7%) who underwent surgery, only 1 patient received neoadjuvant chemotherapy, 8 patients received adjuvant chemotherapy 10 patients (83.3%) received adjuvant radiotherapy. Median Overall Survival (OS) was 46.5 months. In nonparametric analysis, high serum Lactate Dehydrogenase (LDH) and Alkaline Phosphatase (ALP) levels were negatively correlated with OS ($r = -0.73$, $p = 0.004$; $r = -0.71$, $p = 0.006$ respectively). In regression analysis, the increase in death risk was 1.7 times for the patients with high ALP level (not significant statistically, $p = 0.11$), 2.5 times for the patients with recurrent disease ($p = 0.002$). Our study revealed that high baseline LDH and ALP levels might have negative effect on survival in jaws osteosarcoma patients and presence of recurrent disease independently increased risk of death. Due to rarity of this disease, previously reported case series may incorporate in a study to make definite conclusions.

Keywords: Head and neck; Jaws; Osteosarcoma; Prognostic factors; Treatment

Introduction

Head and neck osteosarcomas are seen rarely, account for less than 1% of all head and neck cancers and for about 10% of all osteosarcomas [1-3]. They are mostly located in the maxilla or mandibula [4]. Compared with long bone osteosarcomas, jaws osteosarcomas have lower incidence, later median age, ill-defined multimodality treatment, lower distant metastatic rate, and larger range of 5-year survival (27%-84%) [5-7]. Median age of jaws osteosarcoma is in the fourth decade [3], most common histological subtype is chondroblastic (41%-72%) [8,9], mainstay of the treatment is radical surgery with clear margins whenever technically possible [3,10]. Adjuvant radiotherapy should be regarded for patients with close margins or high grade tumors [3,11]. The role of neoadjuvant and adjuvant chemotherapy is not clear [2,3]. Some prognostic factors such as older age [12,13], increasing tumor size [13,14], osteoblastic subtype [9], tumor positive margins after surgical resection [14] are proposed to be related to poor survival. Due to rarity of jaws osteosarcoma there is lack of knowledge about prognostic parameters and optimal treatment modality. We present 14 adult patients with osteosarcoma of jaws.

Patients and Methods

This study is designed as retrospective analysis of clinical and pathological records of the adult's patients with osteosarcoma of the jaws. Total 14 adult patients with osteosarcoma of jaws identified and treated from August 1997 to August 2011 from 4 different centers in Turkey were evaluated. Clinicopathological variables recorded and analysed were age, gender, date of diagnosis, symptoms at presentation, tumor location, baseline serum Lactate Dehydrogenase (LDH) and serum Alkaline Phosphatase (ALP) levels, histopathological subtype of tumor, grade, maximal tumor diameter, presence of metastasis at the time of diagnosis, preoperative chemotherapy regimen, surgical margin, postoperative chemotherapy regimen, administration of radiotherapy to primary tumor site, presence of relapse, relaps date and site, treatment procedure after relapse, date of last visit or date of death. As age limits for analyzing age as prognostic factor, arbitrarily we used cut off 35. Tumor size limits for analysis were determined as 5cm and 8cm which are used as staging limits in TNM staging of soft tissue sarcomas and bone sarcomas respectively [15]. Relapse Free Survival (RFS) was calculated as the time in months from the date of diagnosis to either the date of recurrence or the date of last follow-up for patients without recurrence. Overall Survival (OS) was calculated as the time in months from the date of diagnosis to either the date of death or the date of last follow-up.

Statistical analyses

Statistical significance was accepted at $p<0.05$. The data were loaded onto the computer with the SPSS 15.0 statistical package software and descriptive statistics (frequence, mean, median), co-relation test and regression test were used as the statistical methods. Means were presented as mean±SD.

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Table 1: Characteristics of patients with osteosarcoma of jaws.

Patient no.	Age	G	Symptom	ALP level	LDH level	Tumor site	Tumor grade	Histological subtype	Tumor size, cm	Neoadj CT	SM	Adj CT	RT	Relapse site	Treatment after relapse	RFS, month	OS, month	Follow-up
1	46	F	swelling	N	N	maxilla	high	fibroblastic	4	-	Tm-	A+P	adj	-		178	178	alive
2	20	M	toothache	high	N	maxilla	high	chondroblastic	7	A+P+Ifos	NO		+	local	CT	11	40	exitus
3	37	M	swelling	high	high	mandibula	high	chondroblastic	10	Mx+A+P	Tm+	-	adj	local	-	6	16	exitus
4	28	M	swelling	N	N	maxilla	high	osteoblastic	4.5	-	NR	-	after recurrence	local	Surgery+RT+CT	4	101	alive
5	27	F	swelling	N	N	mandibula	high	chondroblastic	6	-	Tm-	A+P+Ifos	adj	-		92	92	alive
6	24	M	swelling, pain	N	N	maxilla	high	chondroblastic	8	-	Tm+	-	adj	-		167	167	alive
7	39	F	swelling	N	N	maxilla	high	osteoblastic	9	-	Tm-	A+P	adj	-		142	142	alive
8	38	F	swelling, pain	N	N	mandibula	high	fibroblastic	6	-	Tm+	A+P	-	lung	CT	20	43	alive
9	20	M	swelling, pain	high	N	maxilla	high	chondroblastic	6	-	Tm+	A+P	adj	local	Surgery+CT	19	41	exitus
10	45	F	swelling, pain	high	high	mandibula	high	osteoblastic	6	-	Tm+	A+Ifos	adj	lung	Surgery+CT	7	9	exitus
11	27	M	swelling, pain	N	high	mandibula	NR	NR	NR	-	Tm-	-	neoadj	orbita	CT	6	23	exitus
12	52	F	pain on palate	N	N	mandibula	high	NR	4	-	Tm-	Ifos+Et	-	local	Surgery+CT	26	50	exitus
13	27	M	swelling, pain	N	N	mandibula	intermediate	NR	9	-	Tm-	A+P	adj	local	CT	32	51	exitus
14	17	F	swelling,	-	-	maxilla	high	osteoblastic	8.5	Mx+A+P	NO		+	-		16	16	alive

Abbreviations: G: Gender; ALP: Serum Alkaline Phosphatase; LDH: Lactate Dehidrogenase; Neoadj: Neoadjuvant; CT: Chemotherapy; SM: Surgery Margins; adj: Adjuvant; RT: Radiotherapy; RFS: Relapse Free Survival; OS: Overall Survival; F: Female; M: Male; N: Normal; NR: Not Recorded; Mx: Methotrexate; A: Adriamycin; P: Cisplatin; Ifo: Ifosfamide; Tm: Tumor; NO: Not operated; Et: Etoposide.

Results

A total of 14 patients with osteosarcoma of the jaws were analyzed. Median age was 27.5 years (range, 17-52 years; mean, 31.9 years), 7 patients (50%) were male and 7 patients (50%) were female, corresponding to a ratio of 1:1. Tumor sites of 7 patients were maxilla and remaining 7 were mandibula. Patient and tumor characteristics were shown in Table 1. In the past history of the patients, 1 patient underwent surgery and was administered radiation therapy of 30Gy for giant cell tumor of maxilla 11 years ago; 1 patient underwent excision of maxillary ossified fibroma 9 months ago; 1 patient had history of radiation therapy for retinoblastoma 17 years ago; 1 patient had history of antithyroid medication and thyroidectomy.

The most presenting symptom was swelling and pain at the tumor site (7 patients, 50%), 6 patients presented with only swelling, 1 patient with toothache, 1 patient with pain on palate.

Of the 14 patients, 12 had high grade tumor, 1 had intermediate grade tumor and tumor grade of 1 patient was unknown. Distribution of patients according to histological subtypes was as follows: 5 chondroblastic, 4 osteoblastic, 2 fibroblastic and 3 unrecorded. Of the 13 patients whose serum LDH and ALP levels were recorded, 3 (23.1%) had high LDH levels and 4 (30.8%) had high ALP levels. Mean tumor size was 6.7cm (range, 4-10cm). No patient had distant metastasis at the time of diagnosis. Primary tumor was resected in 12 patients (85.7%), only 1 patient received neoadjuvant chemotherapy, 8 patients received adjuvant chemotherapy. Of the 12 patients who underwent surgery, 5 patients (41.7%) had tumor positive margins. Twelve patients (85.7%) received radiotherapy to primary tumor region: 4 patients for tumor positive surgical margins, 2 for unresected tumor, 1 for local recurrence.

Median follow up time was 96 months (range 17-185 months), 9 patients (64.3%) had recurrent disease. Six patients (66.7%) had local recurrence, 2 patients (22.2%9 had lung metastasis and 1 patient had metastasis to orbital region. Four patients (44.4%) underwent surgery for recurrent disease: 1 for lung metastasis, 3 for local recurrence. Eight patients (88.9%) were received chemotherapy after recurrence. Median RFS was 19.5 months (95% CI, 4-178 months). RFS after 2, 5 and 10 years were 42.9%, 28.6% and 21.4% respectively. Median OS was 46.5 months (95% CI, 9-178 months) and OS after 2, 5, 10 years were 71.4%, 35.7%, 21.4% respectively. Cumulative RFS and OS is shown in Figure 1. As final outcome, 7 patients (50%) were alive, 7 (50%) dead. In nonparametric correlation analysis, final outcome was significantly correlated with ALP level and presence of recurrent disease ($p = 0.025$ and $p = 0.002$ respectively). In regression analysis, the increase in death risk was 1.7 times for the patients with high ALP (not significant statistically, $p = 0.11$), 2.5 times for the patients with recurrent disease ($p = 0.002$). In nonparametric analysis, LDH levels and ALP levels were negatively correlated with OS ($r = -0.73$, $p = 0.004$; $r = -0.71$, $p = 0.006$ respectively), in other words, high LDH and ALP levels associated with lower OS. High LDH levels also correlated with lower RFS ($r = -0\ 0.68$, $p = 0.007$). In regression analysis, the chance of increase in OS time was 1.5 times for the patients with normal ALP levels, and also 1.5 times for the patients with normal LDH levels (not significant statistically, $p = 0{,}159$ and $p = 0.153$ respectively). There was no correlation between survival and other clinicopathological variables (age, gender, mandibula or maxilla localization, histopathological subtype, tumor size, tumor margins after surgery).

Discussion

We analysed data of 14 patients with osteosarcoma of jaws, mean age was 31,9 years and median age was 27.5 years. In literature median age of jaw/cranifacial osteosarcomas were reported with a wide range in the fourth decade, as average 2 decade later than long bone osteosarcomas [3,16]. Unlike osteosarcomas of long bones which

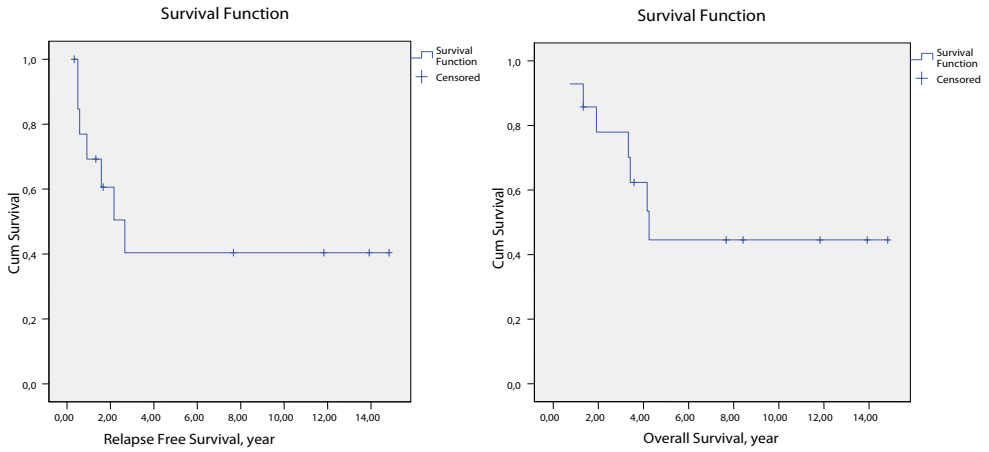

Figure 1: Relapse free survival and overall survival for all patients.

have male predilection, osteosarcomas of head and neck region have equal gender predilection [3,7], as in our study. In a review, slight male preponderance was reported [17]. As tumor site distribution of our patients, a tumor of 7 patients (50%) was in maxilla and 50 % in mandibula. In a study, tumor site was mandibula in 45% of patients and maxilla in 40% of patients [11]. The most common symptom of our patients was swelling with or without pain (80% of patients). Unlike osteosarcomas of long bone which mostly present with pain, osteosarcomas of jaws prensent as swelling rather than pain [16,17].

About past medical history of our patients, 1 patient received radiation therapy for giant cell tumor of maxilla 11 years ago and the other one had history of retinoblastoma and radiation therapy 17 years ago. It was reported that there was a genetic link between osteosarcoma and retinoblastom, and radiotherapy had additional effect to increase risk of developing osteosarcoma [1,3].

Most of our patients (85%) had high grade tumor. Mardinger et al reported that 50% of the jaw osteosarcomas were low grade, [18] but in other studies, majority of head and neck osteosarcomas were reported as high grade [1,11]. Most common histological subtypes of jaw osteosarcomas were chondroblastic and osteoblastic [6,18]. In our study, 45% of patients had chondroblastic subtype and 36% osteoblastic subtype.

In jaws osteosarcomas, distant metastases are seen less frequently and recurrences are mostly as local recurrence [12,17]. None of our patients had distant metastasis at diagnosis and recurrences were mostly as local recurrence (66.7%). In literature, there are variable survival rates within a wide range, 5-year suvival of jaws osteosarcoma ranged between 27%-84% [5-7,14]: 5-year suvival of our patients was 35.7%. Some of the previous studies reported that age may influence prognosis, younger age found to be a positive prognostic factor [12,13]. Some studies showed no statistically significant relation between age and survival [16]. We divided our patients into 2 groups: those younger than 35 years old and those 35 years or older than 35 years, we found no correlation between age and survival, Granowski-LeCornu et al reported that maxillary osteosarcomas had poorer outcome due to the difficulty to achieve clear margins as a result of anatomical localization, leading to increased incidence of residual disease and local recurrence [18]. In another study about head and neck osteosarcoma nonmandibulary primary site found to be a poor prognostic factor [13], whereas 2 other study, similar to our study, reported no statistical difference in survival between maxillary or mandibulary osteosarcoma [16,19].

In our study, tumor size had no effect on survival, but in a previous study tumor size greater than 6cm reported as a poor prognostic factor [13], in another study, increasing tumor size was important predictor of outcome [14].

Some previous studies of long bone or trunk osteosarcomas reported that baseline serum LDH [20] and ALP levels [21] had prognostic significance. Our nonparametric analysis revealed that high LDH and ALP levels significantly associated with lower OS, but their statistical significant did not retain in regression analysis. As far as we know, there is no previous report about the effect of LDH and ALP levels of patients with osteosarcoma of jaws on prognosis.

The primary treatment modality of osteosarcoma of jaw is radical surgery with clear margins whenever technically possible [3,10]. Unlike osteosarcoma of long bones, multimodality treatment for osteosarcoma of jaw is not well defined. Adjuvant radiotherapy should be regarded for patients with close margins, residual, recurrent or unresectable tumors [3,11,17]. Twelve of our patients (85.7%) received radiotherapy to primary tumor region: 4 patients for tumor positive surgical margins, 2 for unresected tumor, 1 for local recurrence.

Some of the previous studies reported that tumor-free resection margin associated with good prognosis [12-14]. Our results did not revealed such association, this may be explained by role of radiation treatment in improving local control for patients with positive margins. The role of neoadjuvant and adjuvant chemotherapy is not clear [2,3]. In a review of 201 patients with craniofacial osteosarcoma, Smeele et al reported that complete surgical removal and chemotherapy were 2 independent significant factors for survival [22]. But in another study, no survival benefit of chemotherapy was found [19]. Our 12 patients (85.7%) underwent surgery, only 1 patient received neoadjuvant chemotherapy, 8 patients received adjuvant chemotherapy.

Given the limitations of the small patient population and retrospective analysis, our study revealed that high baseline LDH

and ALP levels might have negative effect on survival and presence of recurrent disaese independently increased risk of death. Due to rarity of osteosarcoma of jaws, we report a small group of patients, therefore making a definite conclusion is impossible. Previously reported case series may incorporate in a study.

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