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Osteosarcoma of the jaws in Koreans: analysis of 26 cases

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Abstract (J Korean Assoc Oral Maxillofac Surg 2017;43:312-317)

Objectives: In order to assess clinical behavior, response to treatment, and factors influencing prognosis of Korean patients with osteosarcoma of the jaws (OSJ).

Materials and Methods: A retrospective study of clinical, and pathological records of 26 patients with OSJ treated at the Department of Oral and Maxillofacial Surgery in Yonsei University Dental Hospital from 1990 to March 2017.

Results: Of 26 patients, there were 9 men (34.6%) and 17 women (65.4%). Twenty-one of 26 patients had osteosarcoma of the mandible, and 5 of 26 patients had osteosarcoma of the maxilla. The histopathology of OSJ is highly variable, ranging from chondroblastic type (6 out of 26), osteoblastic type (10 out of 26), fibroblastic type (2 out of 26), to the rare variants like mixed type, small cell osteosarcoma types and more. All patients underwent gross total excision and only a few patients underwent neoadjuvant chemotherapy. Postoperative chemotherapy was given to most of the patients as adjuvant treatment or in combination with radiotherapy. The overall survival rate was 73.1% with an overall 2-year survival rate of 83.3%. The overall 5-,10-,15-year survival rates in this study were 73.5%, 73.5%, 49%, respectively. Using Kaplan-Meier analysis with log rank tests, the size of tumor (T-stage), and resection margins were found to affect the survival rate significantly. The chemotherapy was not significantly associated with improved survival rate.

Conclusion: Surgical resection with a clear margin is the most important factor in disease survival. The role of chemotherapy and radiotherapy in OSJ remains controversial, and deserves further studies.

Key words: Osteosarcoma, Maxillofacial, Survival, Mandible, Maxilla

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I. Introduction

Osteosarcomas (OS) are rare, aggressive, and malignant bone tumors that yield osteoid or immature bones. They are highly aggressive and account for approximately 40% to 60% of all primary malignant bone tumors[1,2]. Osteosarcoma of the jaws (OSJ) is extremely rare and it represents only 3% to 4% of all OS. Because of the low incidence of OSJ, it is difficult to assess its treatment protocols and prognosis.

Multimodal treatment for patients with long bone OS has been established well since Rosen et al.[3] introduced neoadjuvant chemotherapy (induction chemotherapy) using a multiagent chemotherapy regimen in the late 1970s. The survival rate for patients with OS in the long bones has improved impressively with a long-term survival rate of 70%[4]. However, the role of chemotherapy in OSJ is unclear and meta-analyses of published data reported conflicting results[5,6]. Adequate surgical resection is a main treatment option for OSJ, although it is difficult to achieve negative surgical margins due to the complex anatomy of the head and neck region[7]. The role of radiotherapy for OS patients is questionable. There are only a few reports about OSJ in Asian countries because of the rarity of the disease. The purpose of this study was to evaluate the incidence and investigate the factors that influenced OSJ prognosis in patients treated at a single institution in Korea.

II. Materials and Methods

This study conforms to the Declaration of Helsinki for

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medical protocols and ethics, and was approved by the regional Ethical Review Board of Yonsei Dental Hospital's Institutional Review Board (IRB No. 2-2017-0018). The informed consent was waived.

A retrospective study of clinical, pathological, and histological records was undertaken for 26 patients with head and neck osteosarcoma treated at the Department of Oral and Maxillofacial Surgery in Yonsei University Dental Hospital (Seoul, Korea) from 1990 to March 2017. Data collected for the study included: age, gender, tumor site, time of presentation, time between tumor presentation and presentation to the clinic, clinical stage, resection margin status, distant metastases, disease recurrence, and follow-up period information. All tumors were staged using the 2010 American Joint Committee on Cancer TNM staging. Statistical analysis was carried out using the IBM SPSS Statistics ver. 23 (IBM Co., Armonk, NY, USA). Kaplan-Meier analysis and log rank tests were used to assess univariate factors and disease-free survival. *P*-values less than 0.05 were considered statistically significant.

III. Results

1. Patients and diagnosis

Of 26 patients, there were 9 men (34.6%) and 17 women (65.4%); the male-to-female ratio was approximately 1.9:1. The mean age of patients in the study was 32 years (range, 10-53 years).(Table 1) The mean follow-up length was 70.7 months (range, 2-259 months). The median time between a patient recognizing the disease and presentation to the clinic was 3 to 4 months. The most common presenting symptom was painless or painful swelling. Other signs were mobile teeth and numbness.(Table 2) The site distributions of the osteosarcoma in the study were as follows: 21 of 26 occurred in the mandible (16 of 21 occurred in mandible body and 5 of 21 occurred in the condyle, coronoid, and ramus) and 5 of 26 occurred in maxilla (3 of 5 occurred in the anterior area and 2 of 5 occurred in the posterior area). In the present histological study, 10 of 26 cases (38.5%) were of the osteoblastic type, 6 cases (23.1%) were chondroblastic type, 2 cases (7.7%) were fibroblastic type, 2 cases (7.7%) were mixed chondroblastic and osteoblastic type, 1 case (3.8%) was small cell type, 2 cases (7.7%) were low grade osteosarcoma, and 3 cases (11.5%) were histologically unclassified types. The summary of these cases is shown in Table 3.

Table 1. Age distribution in relation to diagnosis of osteosarcoma

Age (yr)	No. of patients
10-19	6
20-29	4
30-39	9
40-49	5
50-59	2
Total	26

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2. Treatment

All 26 patients underwent surgical resection and 4 patients received neoadjuvant chemotherapy before surgery and adjuvant chemotherapy. Sixteen patients received adjuvant chemotherapy after surgical resection of the primary lesion. Three patients who had positive margins received postoperative adjuvant chemotherapy and radiotherapy. Of these 3 patients, the patients who had shown disease metastasis from the condyle region to temporal bone received a combination of chemotherapy and radiotherapy treatment. Data on chemotherapy in this study were retrospective and heterogenous with respect to drug regimen and neoadjuvant, adjuvant, or both settings.

3. Prognosis

The overall 2-year survival rate was 83.3%; overall 5-,10-, and 15-year survival rates in this study were 73.5%, 73.5%, and 49%, respectively.(Fig. 1) Tumor (T-stage) size was found to influence survival rate significantly. A study was designed dividing control groups into patients with T1 stage and tumor size less than 8 cm (23 of 26 cases, 88.5%), and patients with T2 with tumor size bigger than 8 cm (3 of 26 cases, 11.5%). The data was analyzed to identify the correlation between tumor size and survival rate using the Kaplan-Meier analysis and log rank test. This showed that tumor size was an important outcome predictor for maxillofacial osteosarcoma (*P*=0.000385).(Fig. 2) Overall, 7 patients had local recurrences with a median time of 14 months after treatment.

Table 2. Clinical symptoms of patients with osteosarcoma

Clinical symptom	No. of patients
Swelling	22
Pain	7
Numbness	5
Tooth mobility	2

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Table 3. Clinical data of the osteosarcoma patients

No.	Gender	Age (yr)	Histologic subtype	Grade	Site	Treatment	Margin status	Location recurrence	Status	F/U length (mo)
1	F	32	N/S	H	Mn	S+CTx+RTx	Positive	LD	DFD	15
2	F	14	Chon	H	Mx	S+CTx	N/A	D	NED	259
3	F	35	Fibro	H	Mn	S+CTx	Free	D	DFD	172
4	F	27	Chon	H	Mn	S	Free	L	AWD	168
5	M	14	Ostb	H	Mn	S+CTx	Positive	LD	DFD	24
6	M	39	Ostb	H	Mx	S+CTx	Positive	LD	DFD	36
7	M	34	Ostb	H	Mn	S+CTx	Free	-	NED	76
8	M	43	Ostb	H	Mx	S+CTx	Free	-	NED	175
9	M	53	Chon	H	Mn	S	Free	-	NED	54
10	M	52	Chon	H	Mn	S	Positive	-	DOC	17
11	F	37	Ostb	H	Mn	S+CTx	Positive	L	NED	107
12	F	45	Mixed	H	Mn	S+CTx+RTx	Positive	D	DFD	31
13	F	19	Mixed	H	Mn	S+CTx	Free	-	NED	100
14	F	36	Ostb	H	Mn	S+CTx	Positive	-	NED	96
15	F	45	N/S	L	Mn	S	Free	-	NED	77
16	M	31	SC	H	Mn	S+CTx	Free	-	NED	73
17	F	41	Chon	H	Mn	S+CTx	Free	-	NED	72
18	M	27	Ostb	H	Mn	S+CTx	Free	-	NED	70
19	M	14	Ostb	H	Mn	S+CTx+RTx	Positive	-	NED	65
20	F	25	Low grade	H	Mn	S+CTx+RTx	Positive	LD	DFD	14
21	F	10	Fibro	H	Mn	S+CTx	Free	-	NED	35
22	F	12	N/S	H	Mn	S+CTx	Free	-	NED	34
23	F	39	Ostb	H	Mx	S+CTx	Free	-	NED	30
24	F	31	Low grade	L	Mn	S	Positive	-	NED	27
25	F	29	Chon	H	Mn	S	Free	-	NED	2
26	F	48	Ostb	H	Mx	S+CTx+RTx	Free	L	AWD	10

(F: female, M: male, N/S: not specified, Chon: chondroblastic, Fibro: fibroblastic, Ostb: osteoblastic, SC: small cell osteosarcoma, H: high grade, L: low grade, Mn: mandible, Mx: maxilla, S: surgery, CTx: chemotherapy, RTx: radiotherapy, N/A: not applicable, LD: local and distant, D: distant, L: local, DFD: dead from disease, NED: no evidence of disease, AWD: alive with disease, DOC: dead of other cause, F/U: follow-up)

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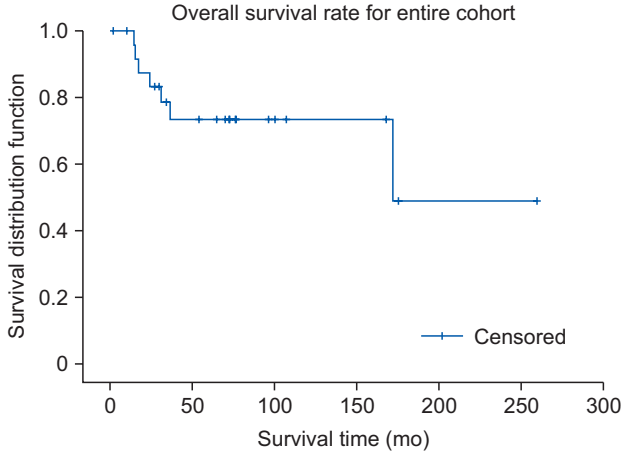

Fig. 1. Kaplan-Meier survival curve. Overall survival; 2-year survival=83.3%, 5-year survival=73.5%, 15-year survival=49%.

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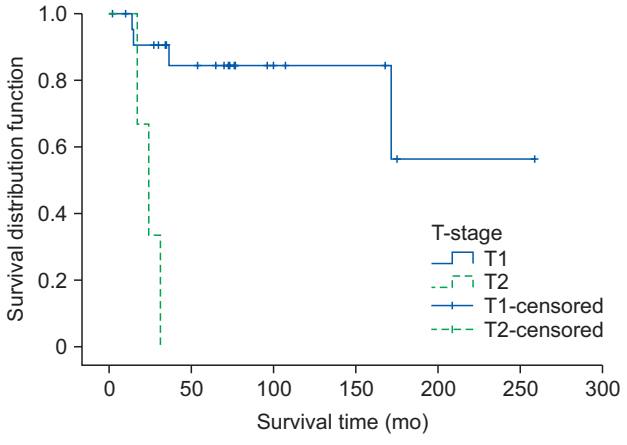

Fig. 2. Kaplan-Meier survival curve. Overall survival by T-stage (size of tumor). *P*=0.000385.

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Five of these cases showed a positive margin status, which was primarily due to difficulties in achieving clear resection margins with complex anatomy and presence of vital organs. Eight patients had distant metastases with a median development time of 2.34 years and in order of decreasing frequency, lung, brain, other bones, and breast were the most common metastases sites. Kaplan-Meier analysis with the log rank test revealed that in 10 of 26 cases, positive margins were the parameter associated with a poor prognosis (*P*=0.001).(Fig. 3) Chemotherapy and radiotherapy were not significantly

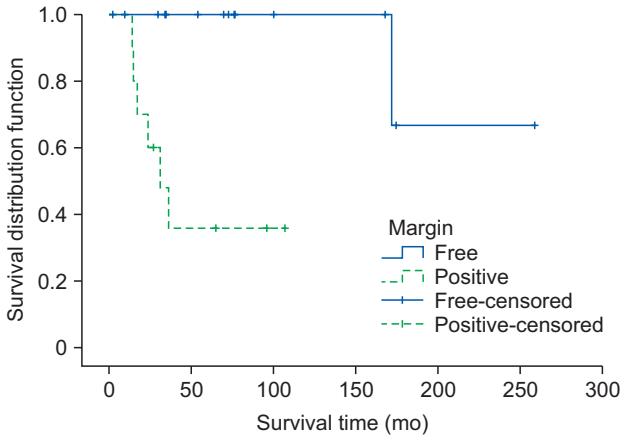

Fig. 3. Kaplan-Meier survival curve. Overall survival by margin status. *P*=0.001.
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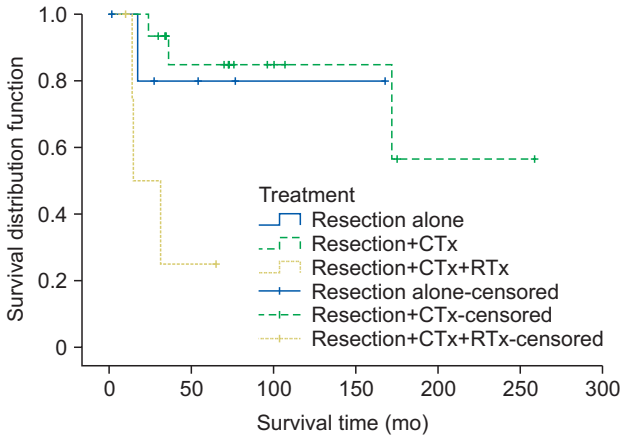

Fig. 4. Kaplan-Meier survival curve. Overall survival by treatment regimen. *P*=0.009. (CTx: chemotherapy, RTx: radiotherapy)
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associated with improved survival rate.(Fig. 4) Therefore, adequacy of local control was found to be the most important predictor of recurrence and survival rates.

IV. Discussion

OSJ are extremely rare and represent only 3% to 4% of all OS[5,8]. The biological behavior of OSJ differs from that of tumors involving other skeletal bones. The mean age at onset for OSJ is two decades later than reported in the extremities, which is in the teenage years, and survival rates are higher[2].

The mean age of patients in our study was 32 years. This is in keeping with data presented in other studies[8,9]. Whereas OS of the extremities shows a slight male preponderance, it is known that OSJs have an equal gender ratio[10]. In the present study, there the female predilection accounted for 1.9:1. The reason for this difference in sex distribution is unclear, but the small cohort may be a factor.

The mandible was involved more than the maxilla (mandible: 21, maxilla: 5). There was no significant correlation between the location of primary lesions and survival, which is consistent with several studies[10-14]. However, positive surgical margins were found to significantly affect survival rate. It was also reported in many other studies that the clear margin is strongly associated with the improved survival rate[15-17].

The most common presenting symptom was a painless or painful lump. Other signs were mobile teeth and numbness. These signs and symptoms could be misdiagnosed as infection, so it is important to maintain an index of suspicion[8].

Several studies reported that a precedent trauma could be an etiologic factor for osteosarcoma. Ajagbe et al.[18] reported that 8 patients remembered having a trauma to the jaws prior to the onset of disease. Kragh et al.[19] reported 2 patients having a history of significant trauma, and in both patients, the trauma had lasted for many years prior to the onset of sarcoma. In the present study, there was no correlation between osteosarcoma and a history of precedent trauma, and yet there was a case in which a female in her forties came to our hospital with a complaint of gingival swelling and tooth pain in the molar region of the mandible. Surgical resection was performed conservatively. She was diagnosed with cement-ossifying fibroma via microscope. After the first surgery, the disease recurred several times over a period of 2 years and 8 months. She was eventually diagnosed with low-grade osteosarcoma transformed from cemento-ossifying fibroma. Cemento-ossifying fibromas are benign tumors, and, although cases of an aggressive type have been reported, no cases of cemento-ossifying fibroma transforming into osteosarcoma have been documented previously[20].

Also, there was a case of a male in his twenties who was histopathologically diagnosed with small cell osteosarcoma; this is a rare histological subtype representing only 1.3% of all OS. It was recommended his small cell osteosarcoma should be treated in a way similar to that of conventional osteosarcoma[7].

The histologic subtype of osteosarcoma was not found to significantly affect survival rate in this study. Hauben et al.[21] reported that specific histological subtypes (i.e., the chondroblastic subtype) were associated with better survival. Conversely, Paparella et al.[22] stated patients with a predominantly chondroblastic pattern had lower survival rates. The histopathologic behavior of osteosarcoma still remains controversial.

OSJ should be treated with radical resection as the primary modality[7,11]. In this study, the most important factor in curative therapy for OSJ was radical resection with clear margins (R0 resection) and the role of chemotherapy was not significantly correlated with survival rates. However, because the data on chemotherapy in this study were essentially small, retrospective and heterogenous with respect to drug regimen and neo-adjuvant, adjuvant, or both, it is difficult to assess the efficacy of chemotherapy for OSJ.

Multimodality treatment of patients with OSJ has been well-established for OS in long bones. Since Rosen et al.[3] introduced the induction chemotherapy into the multimodal treatment regimen of long bone osteosarcoma, its survival rates have impressively improved from 20% in the 1960s to 60% to 70% in the 1980s[7]. Smeele et al.[23] reported that patients with free margins and treatment with chemotherapy had the best survival rates, followed by those with free margins and no chemotherapy. Patients with positive margins and chemotherapy had poor survival rates, but those with positive margins and no chemotherapy had the worst survival rates. The differences among the four groups were statistically significant. Using a proportional hazards model they found that the effects of free margins and treatment with chemotherapy, adjusted for each other, were statistically significant.

It has been reported that the therapeutic role of radiation therapy in OSJ patients was still controversial[1,10,15]. In this study, radiation therapy was used palliatively for recurrent and refractory disease. Because reports on large cohorts of OSJ patients are rare, it is difficult to establish effective treatment protocols. Currently, radical surgery with a clear margin is considered the mainstay of OSJ treatment; however, adequate use of chemotherapy would be beneficial.

V. Conclusion

OSJ is a rare and highly malignant tumor demanding radical treatment. This retrospective study of 26 Korean patients with OSJ found that surgical resection with a clear margin was the most important factor in disease survival. Patients with higher T stage had significantly decreased survival rates. The role of chemotherapy and radiotherapy in OSJ remains controversial, which deserves further study.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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