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Original Article

Gnathic osteosarcomas, experience of four institutions from Turkey

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Abstract: Osteosarcoma is the most frequent primary gnathic sarcoma. Neither the etiology nor the variables effecting the prognosis are fully known due mostly to the rarity of gnathic osteosarcomas. To date a considerable number of clinicopathologic features have been suggested in the evaluation of gnathic osteosarcomas. Still there is a need to experience on several aspects of management. The aim of this study is to report a series of 33 cases of osteosarcoma involving either mandible or maxilla. The clinical, radiological and histopathological features of our cases have usually been non-specific and the most frequent provisional diagnosis were "benign fibroosseous lesion, abnormal mass, giant cell granuloma and benign bone tumor". This non-specific presentation of osteosarcomas of the jaws is compatible with those reported previously. A combined clinical, radiological and pathological study is essential in arriving at the correct diagnosis.

Keywords: Jaw bone osteosarcoma, osteosarcoma, gnathic, oral sarcoma

Introduction

Osteosarcoma is the most common bone matrix forming malignant tumor. Various types of osteosarcoma have been defined according to the main characteristics, such as intramedullary low and high grade osteosarcoma, telangiectatic, small cell and multifocal types. Other entities include; parosteal, periosteal, intracortical, high-grade surface and extraskeletal types [1-4]. Gnathic osteosarcoma is usually regarded as a separate specific entity.

Typical radiologic appearances, frequent involvement of the knee bones and second decade peak are the common characteristics of skeletal osteosarcomas. Jaw bone osteosarcomas constitute about 6-10% of all osteosarcomas and more than 20% of maxillofacial region sarcomas [2-9]. Compared with long bone involvement, gnathic osteosarcomas exhibit more varied clinical and radiologic features. Jaw bone osteosarcomas are characterized by a wider age range and their radiological appearance does not always suggest malignancy as a primary diagnosis [5, 8, 10-12]. Although they are difficult to resect completely, they tend to show a relatively better differentiation and survival rates can be better than the conventional ones. The risk of metastasis is also lower [6, 12].

Jaw bone osteosarcomas are rare tumors and there is a need for larger series for better patient assesment, correct diagnosis and treatment planning. In this study we aimed to report a retrospective series of 33 gnathic bone osteosarcomas diagnosed and managed in four different centers within the last 16 years. We have focused primarily on the clinical and histopathologic features.

Material and methods

Thirty three osteosarcoma cases involving jaw bones diagnosed between 1996 and 2012 were collected from the files of four institutions including Gülhane Military Medical Academy

Table 1. Main clinicopathologic data of the present series

Number	Age-Sex	Location of tumor	Clinical findings	Radiological findings	Provisional diagnosis	Predominant component	Other component(s)	İnitial Diagnose	Follow-up
1	65 F	Maxilla, anterior midline	Large submucosal mass (>5 cm) of one year duration. Mucosal ulceration.	Irregular, mixed radiolucent and opaque areas	Abnormal mass	Chondroblastic	Osteoblastic.	1996	Lost to follow up
2	38 M	Mandibula, corpus	Large ossifying mass (>5 cm).	Irregular ossifying mass and expansion	Fibrous dysplasia	Chondroblastic		1996	Lost to follow up
3	43 M	Mandibula, left corpus	Large, fibroosseous mass (>5 cm). Mucosal ulceration.	Irregular ossifying mass	Fibrooseous lesion	Chondroblastic	Osteoblastic	1997	Lost to follow up
4	55 M	Mandibula right corpus		Irregular destructive mass	Osteosarcoma	Osteoblastic		1998	Recurrence 1 year after operation. No recurrence 2 years after reoperation, then lost to follow up
5	35 M	Mandibula	Swelling	Destructive lesion	Abnormal mass	Chondroblastic		1998	Lost to follow up
6	22 M	Maxilla, left corpus	Palatal large mass (>5 cm) extending to the eye	Destructive lytic irregular lesion	Osteosarcoma	Osteoblastic		1998	Died of disease 1 year after the operation
7	12 F	Mandibula, right corpus	Large (>7 cm), fragile mass, teeth displacement. Mucosal ulceration.	Destructive, lytic mass	Giant cell granuloma, Sarcoma	Fibroblastic		1999	Lost to follow up
8	38 M	Mandibula left corpus	Large vestibular swelling (>4 cm). Mucosal ulceration.	Destructive lytic mass	Giant cell granuloma, Ameloblastoma	Osteoblastic	Chondroblastic	2000	Lost to follow up
9	22 M	Maxilla, palatal	Maxillary mass and palatal swelling for two months. History of retinoblastoma when 6 months of age.		Abnormal mass	Osteoblastic		2000	Lost to follow up
10	28 F	Mandibula corpus	Swelling, facial asymetry	Radiopaque mass related with teeth	Cementoblastoma	Osteoblastic		2000	Leimyosarcoma developed after osteosarcoma diagnosis. Lost to follow up
11	50 F	Maxilla, posterior	Asymptomatic swelling for three months (>4 cm). Mucosal ulceration.	Destructive lytic and opaque mineralized areas	Abnormal mass	Chondroblastic	Osteoblastic and fibroblastic	2000	Died of disease 2 years after the operation
12	18 F	Maxilla	Painful and ulcerated palatal swelling involving tuber maxilla and sinus (>5 cm).	Destructive mass filling the maxillary sinus	Giant cell granuloma, Malignant tumor	Chondroblastic		2000	Lost to follow up
13	74 M	Mandibula, anterior	Large mass involving floor of mouth and labial mucosa (>4 cm). Mucosal ulceration.	Radiolucent destructive mass	Giant cell granuloma, Osteosarcoma	Osteoblastic	Giant cell and telengiectatic	2001	Died of disease 1 year after the operation
14	62 F	Maxilla, right tuber area	Destructive mass, tooth resorption	Destructive and lytic lesion	Abnormal mass	Chondroblastic		2001	Lost to follow up
15	58 F	Maxilla, right	Large mass involving maxillary sinus.	Destructive lesion	Osteosarcoma	Osteoblastic		2002	Recurrence 2 years after the operation. Died of disease 2 years after the reoperation.
16	27 M	Maxilla, anterior	Large swelling.	Destructive lytic lesion	Malignant tumor	Fibroblastic		2002	Lost to follow up

17	20 M	Maxilla and left face bones	Large mass (>7 cm). Mucosal ulceration.	Destructive lesion involving maxilla, zygomatic and temporal bones	Large abnormal mass	Osteoblastic		2003	Lost to follow up
18	24 M	Maxilla, right	Large demarcated mass for two months and buccal swelling (>4 cm). Mucosal ulceration.	Dens, radiopaque mass involving maxillary sinus	Osteoma	Chondroblastic	Osteoblastic	2003	Recurrence 2 years after the operation, Died of disease 1 year after reoperation
19	20 M	Mandibula	Large mass.		Osteosarcoma	Chondroblastic		2004	Lost to follow up
20	63 M	Mandibula, left corpus	Large mass with submandibular extension.		Soft tissue mass with cortical bone irregularity	Osteoblastic		2004	Lost to follow up
21	27 F	Mandibula, right corpus	Painful swelling at the tooth extraction area.	Lytic and sclerotic irregular mass	Ossifying fibroma	Chondroblastic		2004	Lost to follow up
22	9 F	Maxilla, left	Large expansive mass causing teeth displacement.	Sclerotic irregular mass displacing tooth germ	Abnormal mass	Osteoblastic		2005	Lost to follow up
23	14 F	Maxilla, left	Large mass (>5 cm)			Chondroblastic		2005	No evidence of disease
24	20 M	Mandibula, right corpus and ramus	Large mass.	Destructive radioopaque mass and soft tissue extention	Osteosarcoma	Osteoblastic		2007	No evidence of disease
25	23 M	Maxilla, posterior and palatal	Palatal and vestibular swelling. Mucosal ulceration.	Irregular mass	Pleomorfic adenoma	Fibroblastic	Osteoblastic	2007	No evidence of disease
26	35 M	Mandibula, alveolar arch	Large ulcerating mass	Destructive, lytic lesion with soft tissue extension	Granulation tissue, malignancy	Fibroblastic		2007	Died of disease 9 months after the operation
27	F	Mandibula, right corpus and ramus	Large mass and history of operation with the diagnosis of osteochondroma.	Irregular mass	Osteochondroma	Chondroblastic		2007	Died of disease 2 years after the operation
28	28 F	Mandibula corpus	Swelling noticed within last 4 months.	Irregular mass with large sclerotic zones	Fibrous dysplasia	Chondroblastic		2008	No evidence of disease
29	24 M	Mandibula corpus	Mucosal ulceration and swelling	Irregular opaque mass	Ossifying fibroma	Fibroblastic		2008	No evidence of disease
30	45 F	Mandibula, left	Abnormal swelling	Mass with soft tissue extention	Mixt tumor	Fibroblastic		2008	Recurrence in 2009 and reoperated
31	15 F	Maxilla, right	Abnormal swelling	Ground glass appearance	Fibrous Dysplasia	Chondroblastic		2008	No evidence of disease
32	30 M	Mandibula, posterior	Expansive mass	Bone and soft tissue mass	Chondrosarcoma	Chondroblastic		2009	No evidence of disease
33	57 F	Maxilla, right	Expansive mass extending into maxillary sinus	Irregular mass with opacities	Ossifying fibroma	Chondroblastic		2010	Recurrence in 2012 and reoperated

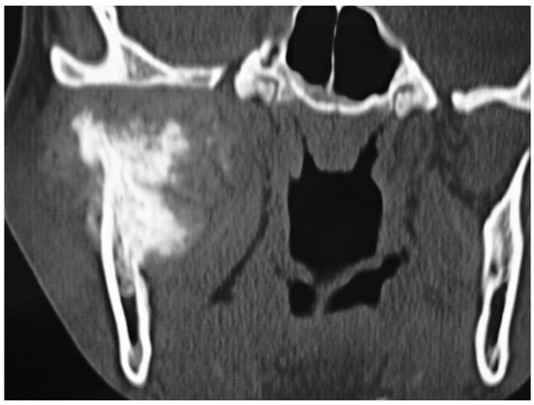

Figure 1. Osteosarcoma involving right ramus mandibula shows irregular soft tissue extention (case 21).

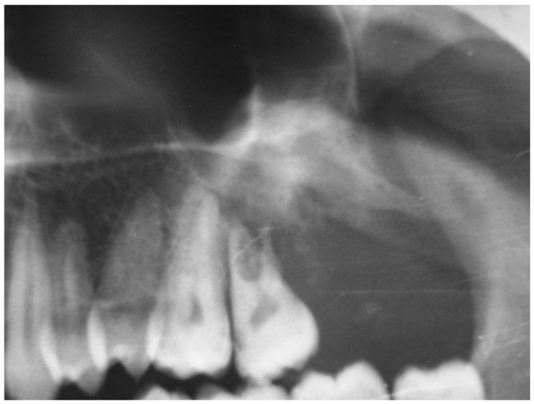

Figure 2. Lytic and destructive lesion in the left maxillary tuber and molar tooth area with root resorption (case 11).

(11 cases), Gören Pathology Laboratory (17 cases), Dicle University School of Dentistry (4 cases) and Atatürk Education and Research Hospital (1 case). All available hematoxylin and eosin stained histologic slides were retrieved from files and reevaluated by pathologist authors. Additional cuts were made from paraffin blocks when necessary. The clinical and radiographic data were compiled and briefly presented in **Table 1**. Authors were able to re-examine the radiographic studies in most cases.

Results

Jaw bone osteosarcomas in this series showed a slight mandibular predilection (**Table 1**). Tumors were seen particulary around the eight molar tooth, the posterior actively growing areas of the mandibula and maxilla. The most

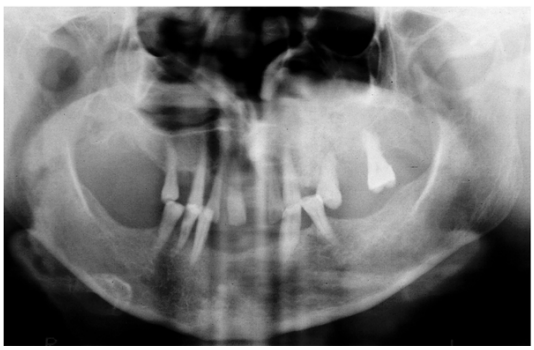

Figure 3. Large destructive tumor in the left maxilla and extention into the maxillary sinus (case 12).

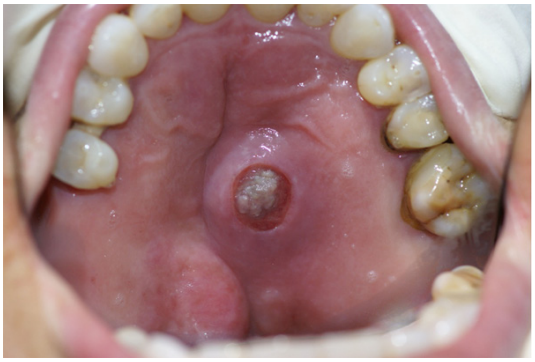

Figure 4. Palatal mass and ulceration due to maxillary osteosarcoma (case 9).

frequent (eight cases) presumptive clinical and radiologic diagnosis was “abnormal mass lesion” (**Table 1**). Benign fibroosseous lesion, giant cell granuloma, benign bone tumor and malignant tumor were the other provisional clinical diagnoses of our gnathic osteosarcomas. A panoramic radiograph was available in most of the cases and destructive, irregular mass with radioopaque and radiolucent areas were seen (**Figures 1**-**3**). Sunburst pattern typical for long bone osteosarcomas were less evident in our jaw bone osteosarcomas.

Swelling with overlying mucosal ulceration was the most common symptom in our series. Some lesions presented in the form of a nodular submucosal mass (**Figure 4**). Pain and teeth extraction related difficulties were also noted. Invasion and widening of periodontal ligament (Garrington’s sign) was seen in one of our cases (**Figure 5**). Tooth structures have usually been resistant to destruction (**Figure 5**). Most of the childhood (<20) or young adult patients’ (<30) osteosarcomas were seen in maxilla in the

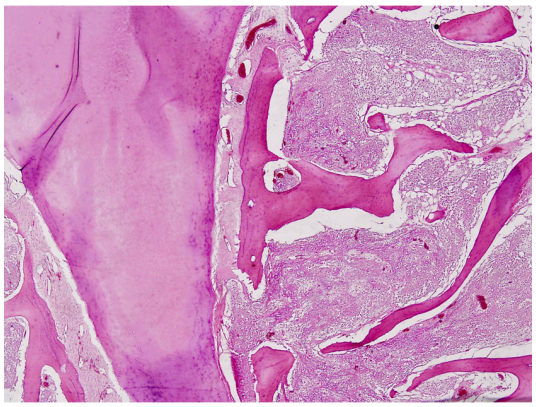

Figure 5. Osteoblastic type jaw bone osteosarcoma invasion into the periodontal space. Tooth seems resistant to tumor invasion (HE, ×50).

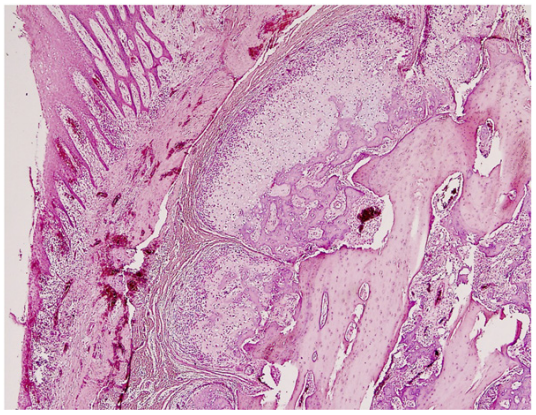

Figure 6. Histopathology of jaw bone osteosarcoma revealed lobulated submucosal chondroblastic type osteosarcoma and alveoler bone invasion (HE, ×50).

present series. Maxillary osteosarcomas were more frequent in females and histologically most of them were chondoblastic. Chondroblastic osteosarcoma was the most frequent histologic type. A subepithelial, lobulated, well-differentiated chondroid tissue was the characteristic histologic appearance of chondroblastic osteosarcomas (**Figure 6**). Radiologically, chondroblastic histologic type exhibited a low attenuation soft tissue component. More than one histologic component, including telengiectatic and giant cell areas, were seen in some of our cases. A case of fibroblastic, well-differentiated osteosarcoma caused papillomatous changes on the surface of the mucosa (**Figure 7**). This case was compatible with parosteal type osteosarcoma with medullary infiltration. Follow-up data is only available for some of the cases due to incomplete medical records

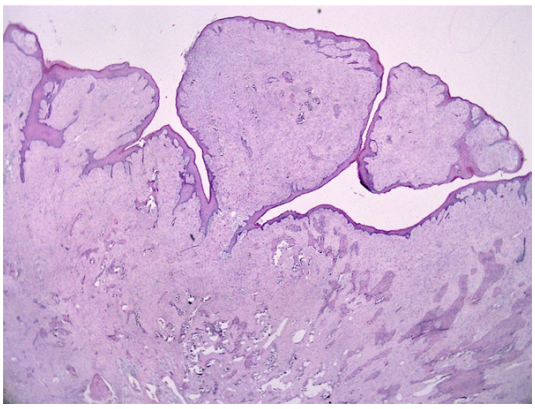

Figure 7. Papillomatous change on the oral mucosa caused by well-differentiated fibroblastic osteosarcoma (case 25) (HE, ×50).

(**Table 1**). As far as we know from our follow-up data and clinical practice, local recurrences were more frequent than metastasis and they arised within the first years of surgery.

Discussion

Gnathic osteosarcomas are rare, malignant tumors. Mandibular body and maxillary alveolar ridge are the most predominantly involved sites. Among the conditions which were suggested as aetiologic factors are the following: Growth abnormalities of tooth bearing jaws, eruption related problems, chronic trauma and inflammations, radiation exposure, polyostotic fibrous dysplasia and Pagets disease of elder patients. Li-Fraumeni syndrome and familial retinoblastoma patients show a genetical tendency to development of osteosarcoma [2-5, 8, 13]. Most of the series offer no known predisposing factor for the jaw bone osteosarcoma [6, 7]. Fernandes et al. [8] reported that risk factors in their series of 16 patients with jaw bone osteosarcoma were 1 case of Li-Fraumeni syndrome, 1 case of polyostotic fibrous dysplasia and 1 case with history of radiation theraphy to the head and neck for a thyroid malignancy [8]. Except for a single case, a 22 years old male (case 9) who had a history of retinoblastoma excision, there were no other known predisposing factors in this series of cases. In one of our cases (case 10) who is thought probably be syndromatic but not had a chance to prove it, a leiomyosarcoma was developed in the wall of vena cavae inferior after he had been diagnosed and treated osteosarcoma in jaw.

In the study of Granowski-Lecornu et al., mandibular osteosarcoma was found predominantly in female patients [14]. On the contrary, mandibular osteosarcoma was seen predominantly in male patients (M/F: 12/6) and maxillary ones were more frequent in females (F/M: 9/6) in this study. The age range of gnathic osteosarcomas is wider than those of extragnathic osteosarcomas [5, 8, 10-12]. In our cases, the age range was between 9 and 74. It is reported that, childhood head and neck osteosarcomas were seen more frequently in mandibula [13, 15, 16]. In our younger patients (<20) the tumor involved frequently the maxillary bone. (**Table 1**) Gadwal et al. suggested that head and neck osteosarcomas in pediatric population frequently involved the mandible and were typically of low to moderate grade [16]. August et al. reported that, in their series, higher age was statistically associated with decreased survival [10]. Lee et al. reported that atypical radiologic features are especially more common in older patients [17]. In elder patients osteosarcomas mimic benign tumors more frequently, infections and other malignancies such as metastatic tumors compared with those in adolescents [17]. Therefore, osteosarcomas in elder patients can be overlooked or misinterpreted easily.

Jaw bone osteosarcomas usually presented with non-specific clinical and radiologic features. The most common symptoms and findings were jaw bone swelling, mucosal ulceration, submucosal mass, pain and nasal obstruction. Radiologic findings were rarely diagnostic. The anatomic structure of the face, the continuity of the bones with sinuses and the teeth can make the radiologic evaluation of this area difficult. The initial clinical and radiological diagnosis was benign fibroosseous lesion or benign bone tumor in 10 cases; giant cell granuloma in 4; and abnormal mass lesion in 8 patients (**Table 1**). Osteosarcoma or malignant tumor was provisional diagnosis in 11 cases. Most of the lesions were located within the posterior tooth bearing areas. The exact site could not be detected in large and destructive tumors. Odontogenic inflammations and other odontogenic lesions have also been considered in the clinical differential diagnosis. Irregular bone growth with sunburst pattern and a poorly defined destructive and lytic appearance were the main radiologic findings for jaw bone osteosarcomas as in long bones. Most of the jaw bone osteosarcomas are intramedullary tumors with extraskeletal extention. Compared with long bone osteosarcomas, gnathic ones are less distinctive. Surface, periosteal, parosteal and other special types of osteosarcomas have also been reported [15, 18] Sawair et al. reported 9 cases of periosteal osteosarcoma of the jaw bones an one of them shows intramedullary involvement [15].

Conventional radiographs are of limited value in evaluating the head and neck osteosarcomas due to the presence of superimposed bony structures [19, 20]. Computed tomography provides important information about tumor matrix and can help detecting cortical destruction. Magnetic resonance imaging appears to be superior in defining intramedullary and extraosseous extentions. Determination of the pre-and post treatment extent of neoplastic involvement of dentomaxillofacial complex and paranasal sinuses helps in evaluating the response of the tumor to theraphies. Osteosarcoma of the jaw bones may show radiologic features similar to the benign tumors of the jaw bones [12]. In the absence of bone destruction, osteosarcomas may simulate some benign cementoosseous lesions of the jaw [12, 13]. Correct and detailed imaging interpretation of processes involving the jaw bones may narrow the broad radiologic differential diagnosis and improves patient management [20].

Chondroblastic type osteosarcoma presented with submucosal nodular swelling was the most common histologic type in our series (**Table 1**). Most of them show both a large surface mass and a medullary extension. At least some of them may be periosteal type osteosarcoma and this may not be as rare as it is thought. This may partially explain the intermediate prognosis of jaw bone osteosarcomas. Longest survival is obtained for histologically low grade mandibular tumors [21]. Winston et al. reported that osteoblastic form was the most common subtype in 12 cases of children and young adult jaw osteosarcoma [22]. In the present cases, chondroblastic subtype was also the predominant feature among 8 pediatric and young adult patients (<30 years of age).

The single most important histologic finding in the diagnosis of osteosarcoma is the presence of atypical osteoid and/or tumor bone produc-

tion. Similar to the previously reported series [6, 13, 23], chondroblastic appearance was the most frequent histologic feature in our cases (**Table 1**). Predominantly osteoblastic and fibroblastic cases were less common and usually seen in mandibula. Histologic typing of osteosarcomas is subjective and the dominant component has occasionally been declared as the histologic type. In some of our cases, more than one component, including telengiectatic and giant cell areas were seen. Presence of these different components were noted as microscopic details. Although there have been attempts of histologic grading for osteosarcomas, the reproducibility is poor [24]. Jaw bone osteosarcomas are usually considered as intermediate grade tumors and most of them show a better prognosis compared to long bone and extragnathic craniofacial bone osteosarcomas. Paget's disease related jaw bone osteosarcomas are, however, agressive tumors [25]. Craniofacial fibrous dysplasia and ossifying fibroma with highly cellular stroma must be considered in the histologic differential diagnosis of well-differentiated gnathic osteosarcomas. Intramedullary well-differentiated osteosarcoma frequently mimics benign bone lesions. Neoplastic bone in well-differentiated osteosarcoma cases may be oval or round that mimicked cementum [26]. This may cause to misinterpretation to benign fibroosseous lesions. As seen in **Figure 7**, some of our cases were very similar with benign fibrooseous lesions in histopathological examination and it was challenging to establish the proper diagnosis. We have also seen a case of cementoblastoma of tooth bearing mandible which was an actively growing lesion with formation of parallel new bone trabeculae rimmed by epitheloid cementoblasts, yet, misdiagnosed as a jaw bone osteosarcoma. Occasionally, a tumor displaying overlapping features of a variety of biologically different lesions fails to be identified specifically. Koury et al. suggested the use of the term "atypical fibroosseous lesion" as a working diagnosis for these lesions which may include some osteosarcomas [27].

The two main prognostic criteria of gnathic osteosarcomas are the tumor size and the resectability at presentation [16]. Wide surgical resection is the primary treatment modality for jaw bone osteosarcomas. However, marginal exicision is unavoidable in some jaw bone osteosarcomas due to anatomic difficulties [13]. Complete resection of tumors involving the maxillary bone is especially difficult and local recurrence is more frequent than mandibular ones. Reoperation is frequent for gnathic osteosarcomas. Local recurrence was more common than distant metastasis in jaw bone osteosarcomas and positive margins were strongly associated with poor prognosis [10, 11]. None of our patients initially presented with lung metastases. Death is usually associated with local tumor extentions [6]. Most of the tumors in the present series were delayed and many of them were larger than 4 cm in largest diameter.

In our institutions; patients with long bone ostesarcomas are given preoperative neoadjuvant chemotheraphy and then en-bloc resection is performed when possible. Cisplatin, ifosfamide, adriamycin and occasionally etoposide are the effective and preferred chemotherapeutics for osteosarcomas. Radiotheraphy is not a preferred treatment modality for long bone osteosarcomas. According to the degree of effectiveness of chemotheraphy on resection specimens, further adjuvant chemotheraphy is planned. The effectiveness of the above treatment modality on gnathic osteosarcomas is not known and there is insufficient information on patient survival after neoadjuvant chemotheraphy. Granowski-LeCornu et al. [14] reported that neoadjuvant chemotheraphy is not clearly beneficial for survivial of jaw osteosarcoma patients [14]. Since gnathic osteosarcomas are less frequent tumors, surgical intervension is the first and the preferred procedure at our institutions. Only adjuvant chemotheraphy is given to the gnathic osteosarcoma patients after surgery. Chindia stated that, advent of adjuvant and neoadjuvant chemotheraphy as an adjunct to radical surgery has greatly improved the prognosis of jaw bone osteosarcomas [5]. Similarly, August et al. reported that patients receiving chemotheraphy showed a trend toward better survival [10]. Canadian study group declared that there is a trend toward better prognosis in those who received chemotherapy in addition to surgery [11]. Thiele et al. suggested that combined treatment of radical resection of the tumor with high dose chemotheraphy according to standard protocols is the most effective treatment for craniofacial osteosarcomas [9]. On the

other hand, Mardinger et al. reported that chemotherapy did not dramatically alter the prognosis of osteosarcoma and the effect of radiotheraphy was uncertain [6]. The effect of adjuvant chemotheraphy in controlling locoregional disease seems higher than radiotheraphy [6]. Unlike long bone osteosarcomas, frequent local recurrences increase the use of radiotheraphy on gnathic osteosarcomas. As a recent consideration; Guadagnolo et al. suggested that adjuvant radiotheraphy following surgery has been found effective for the treatment of jaw/craniofacial region osteosarcomas [28]. Postoperative radiotheraphy (60-70 Gy) is a routine application in our hospitals due to the difficulty of resection with safe margins. Our series provide limited information about the treatment results and prognosis only in some of our cases due to some difficulties of follow-up (**Table 1**).

The age range, histologic types, tumor locations and sypmtoms of our cases are not significantly different from those in the previous reports. The frequent provisional clinical diagnoses such as abnormal mass, benign fibroosseous lesion, giant cell granuloma and malignant tumor, reflect the non-specific clinical and radiological appearances of osteosarcomas in this region. The large spectrum of jaw bone lesions, the complex anatomic structure and the wide age range magnify the problems. Clinicians should be aware of this difficulty. Further series of gnathic osteosarcomas may improve the knowledge on different presentations and help designing better treatments.

Disclosure of conflict of interest

None declared.

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