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ORIGINAL ARTICLE

Clinicopathological analysis of osteosarcoma of jaw bones

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OBJECTIVES: To identify clinicopathological characteristics and prognosis of osteosarcoma of the jaw bones (JOS) and to compare the data with results of similar studies. To study the effectiveness of different treatment modalities currently available for this malignancy.
SUBJECTS AND METHODS: Nineteen cases of JOS diagnosed from 1993 to 2003 were retrieved from the departmental archives. These were categorized into histopathological subtypes and graded according to the severity of the malignancies and the data analyzed. Fourteen cases were followed up and the success rate with different treatment modalities assessed.
RESULTS: The mean age for JOS was 34.1 years. There were 11 mandibular lesions and eight maxillary lesions. Osteoblastic variant (53%) was the commonest histopathological subtype. High grade (grades III and IV) was more prevalent. All 14 followed up patients underwent surgical excision – five with adjuvant radiotherapy and six with adjuvant chemotherapy. Local recurrence was the commonest complication. Nine of the 14 were surviving with a survival rate of 64.2% for a median follow-up period of 5.25 years.
CONCLUSIONS: JOS is a distinct group of lesions with a better prognosis if diagnosed and treated early. It does not show any ethnic variability. Existing histopathological typing and grading may not indicate the prognosis of JOS. Adjuvant chemotherapy is a better treatment modality than adjuvant radiotherapy.
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Keywords: osteosarcoma; jaw bones

Introduction

Osteosarcoma (OS) is a primary malignant bone tumor characterized by the direct formation of bone or osteoid by tumor cells (Schajowicz, 1993). It is the second most common primary malignant bone tumor accounting for about 20% of all bone tumors (Unni, 1996). The average incidence of new cases of osteosarcomas per year is 0.07 cases per 100 000 population (Garrington *et al*, 1967). Preferentially, osteosarcomas affect the most rapidly growing parts of the skeleton; metaphyseal growth plates in the femur, tibia and humerus being the commonest sites. OS occurring in the jaw bones is rare, comprising only 6.5% of all OS (Garrington *et al*, 1967). Sometimes referred to as gnathic OS, it has some biologic aspects different from OS of long bones, such as older age at presentation, longer median survival, rare metastases and local recurrences difficult to control. In JOS, local recurrence is common (Forteza *et al*, 1986) and is often uncontrollable, typically leading to the death of patients. Distant metastases are less frequent (Garrington *et al*, 1967) than in other OS types and the 5 year survival rate is approximately 40% (Clark *et al*, 1983).

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Subjects and methods

Nineteen cases (10 men, nine women) with a histopathological diagnosis of osteosarcoma of jaw bones, during the period 1993–2003 were included in the study. Supportive and follow-up clinical and histologic material was obtained whenever possible from the referring clinicians. Hemotoxylin and eosin sections were prepared for all the cases in order to re-classify and grade according to WHO and Broders' criteria, respectively. The data were analyzed with regard to age, gender, site, histopathologic type and histopathologic grade. Five patients were lost to follow-up. Therefore, only 14 cases were followed up, with regard to different treatment modalities adopted, complications, survival, and prognostic factors (Figures 1 and 2).

These 19 cases are discussed in light of a comprehensive review of 824 cases reported in the medical literature over the past three decades.

Results

The mean age of presentation of primary tumors was 34.1 years with an age range of 12–69 years. Seventeen cases occurred before the fifth decade. (Clark *et al*, 1983)

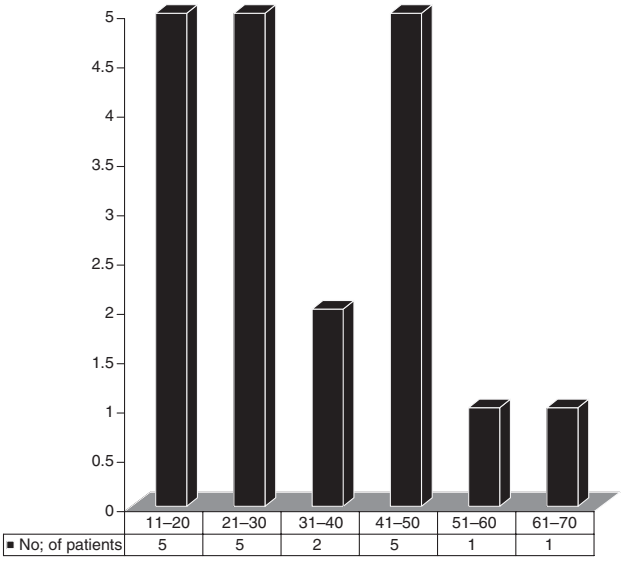
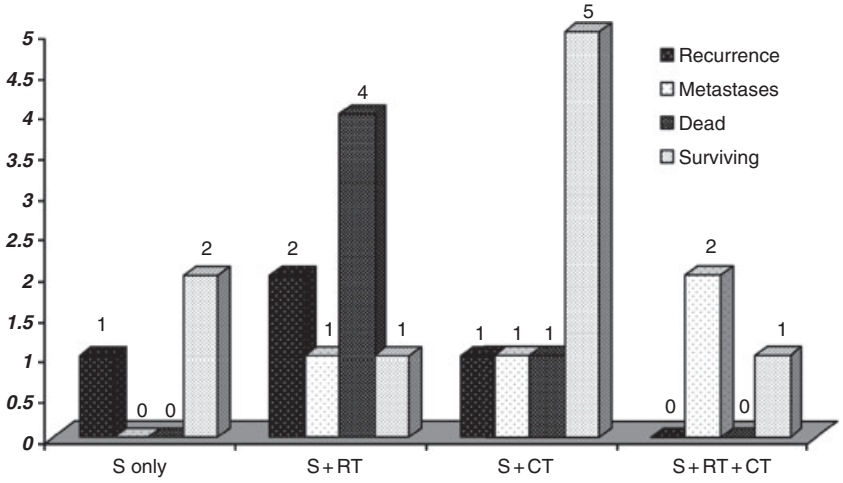


Figure 1 Chart showing the age distribution of JOS in our study

There was no marked gender predilection, with a male:female ratio of 1.1:1. The mean age of presentation among women was 29.6 years and among men it was 38.1years. Eleven (58%) had tumors in the mandible and eight (42%) had tumors in the maxilla. The mean age of presentation of mandibular lesions was 32.09 years and in maxillary lesions it was 36.8 years. Mandibular lesions showed a peak incidence in the second decade of life and in maxillary lesions the peak age was between the third and fifth decades.

Histopathologically, the dominant variant was osteoblastic type (OOS) with 10 cases(53%), followed by eight cases (48%) of chondroblastic type (COS) and one case (0.5%) of fibroblastic type (FOS). According to the analysis of 10 OOS, (five men, five women) six were in the mandible and four were in the maxilla. The age ranged from 16 to 50 years. When considering COS (five men, three women), mandible and maxilla were equally affected with an age range of 12–69 years. FOS occurred in the mandible of a 42-year-old female. There was no characteristic epidemiologic distribution between different histopathologic types. Histopathologic grades revealed 11 (58%) high grade (grades III and IV) cases and eight (42%) low grade (grades I and II) cases, with a high grade to low grade ratio of 1.37:1.0. However, of the four grades, grade II had the highest prevalence with seven cases (37%). Of the low grade cases, only three were from the maxilla and the rest from the mandible. Low-grade osteosarcomas had higher prevalence in the mandible, although the high-grade cases did not show such a significant difference. Data of the 19 patients included in the study are summarized in Table 1.

Treatment and follow-up information was available for 14 of the 19 patients (seven men, seven women) Table 2. The follow-up period ranged from 6 months to 10 years. All patients underwent surgical resection – six with adjuvant chemotherapy, five with adjuvant radiotherapy, and one with both radiotherapy and chemotherapy. There was lack of uniformity in the treatment protocols applied by different clinicians. Different treatment modalities had a marked bearing on the survival of patients. The patients who were treated with surgery and adjuvant radiotherapy had a poorer survival rate of 20% after a median follow-up period of 3 years, compared with the six patients who underwent surgery and adjuvant chemotherapy, who showed



Rx type	No. of pts	Average Follow up	Survival rate (%)
S only	2	1.25 (yrs)	100
S + RT	5	3.0 (yrs)	20
S + CT	6	5.25 (yrs)	83.3
S + RT + CT	1	2.0 (yrs)	100

Figure 2 Overall treatment evaluation of 14 patients

Table 1 Clinical data of the 19 patients in our study

	Age	*Sex*	*Race*	*Site*	*Histopath type*	*Grade*	*Treatment*	*Follow-up*
1	17	F	S	mn	OOS	2	Ex + CT	Dead
2	35	M	Mu	mx	COS	3	Unknown	Unknown
3	16	M	T	mn	OOS	1	Unknown	Unknown
4	47	F	S	mn	OOS	2	Unknown	Unknown
5	20	F	S	mn	OOS	4	Ex + RT	Dead
6	28	F	S	mx	OOS	3	Ex + RT + CT	Surviving
7	30	M	T	mx	OOS	2	Unknown	Unknown
8	12	F	S	mn	COS	4	Ex + CT	Surviving
9	41	M	S	mx	COS	2	Ex + RT	Dead
10	69	M	S	mn	COS	2	Unknown	Unknown
11	42	F	S	mn	FOS	4	Ex + RT	Dead
12	25	F	S	mn	COS	2	Ex + CT	Surviving
13	56	F	T	mn	COS	3	Unknown	Unknown
14	29	M	S	mn	OOS	3	Ex only	Unknown
15	20	F	S	mn	OOS	3	Ex + CT	Surviving
16	38	M	S	mx	COS	4	Ex	Surviving
17	48	M	S	mx	OOS	4	Ex + RT	Surviving
18	50	M	T	mx	OOS	4	Ex + CT	Surviving
19	25	M	Mu	mx	COS	2	Unknown	Unknown

F, female; M, male; S, Sinhala; T, Tamil; Mu, Muslim; mn, mandible; mx, maxilla; OOS, osteoblastic osteoblastoma; COS, chondroblastic osteosarcoma; FOS, fibroblastic osteosarcoma; Ex, excision; RT, radiotherapy; CT, chemotherapy.

Table 2 Follow-up data of 14 patients

	Age	*Sex*	*Histopath*	*Grade*	*Rx*	*Follow-up*	*Time*	*COD*	*Rec Time*	*Histology*	*Metastases*	*Time*
1	17	F	OOS	2	Ex + CT	Dead	1 year AS	Lung M	N		1 Lung	1 year AS
2	20	F	OOS	4	Ex + RT	Dead	6 month AS	Leg M	N		1 leg	6 month AS
3	28	F	OOS	3	Ex + RT + CT	Surviving	4 years		N		2 lung + leg	1&2 years AS
4	12	F	COS	4	Ex + CT	Surviving	4 years		N		N	
5	41	M	COS	2	Ex + RT	Dead	1 year AR	Rec	Y 1 year AS	COS3	N	
6	69	M	COS	2	Ex + CT	Surviving	2 years		Y 2 years AS	COS3	N	
7	42	F	FOS	4	Ex + RT	Dead	3 years	Unknown	N		N	
8	25	F	COS	2	Ex + CT	Surviving	2 years		Y 1.5 years AS	OOS1	N	
9	29	M	OOS	3	Ex only	Surviving	2 years		N		N	
10	20	F	OOS	3	Ex + CT	Surviving	1.5 years		N		N	
11	38	M	COS	4	Ex only	Surviving	1 year		N		N	
12	48	M	OOS	4	Ex + RT	Surviving	1 year		N		N	
13	50	M	OOS	4	Ex + CT	Surviving	2 months		N		N	
14	30	M	OOS	2	Ex + RT	Dead	1 year AR	Rec	Y 1 year AR	OOS3	N	

Rx, treatment; AS, after surgery; AR, after recurrence; Rec, recurrence; Y, yes; N, no; COD, cause of death; M, metastases.

83.3% survival rate after a median follow-up period of 5.25 years (Table 3). This highlights the fact that surgical excision with adjuvant chemotherapy is a better treatment modality than adjuvant radiotherapy.

The commonest complication was local recurrence (four of seven complications in 14 patients). Three of the four recurrences occurred in men and were of COS. Two of them had died due to uncontrollable local spread and had had surgery and adjuvant radiotherapy as treatment. Most recurrences had the same histopathologic type as the primary but the grade had been characteristically increased. Majority of the recurrences occurred within 2 years after primary excision. There were three distant metastases, which occurred in women below 30 years and were of osteoblastic type. The commonest sites were lungs and long bones and occurred within a year after primary surgery. Two of the four who had had surgery and radiotherapy as treatment died as a result of metastatic spread. Of the 14 patients who were followed up for a median follow-up period of 5.25 years, five died. The average survival period was 2.25 years with a survival rate of 64.2%. Majority of the deaths were in

Table 3 Survival rates for different treatment modalities

Treatment modality	*No. patients*	*Average follow-up (years)*	*Survival rate (%)*
Surgery only	2	1.25	100
Surgery + chemotherapy (CT)	6	5.25	83.3
Surgery + radiotherapy (RT)	5	3.0	20
Surgery + CT + RT	1	2.0	100

the osteoblastic type and in those who had had surgery and radiotherapy as treatment. There was no obvious relationship between different histopathologic grades and patient survival. However, taken together, stage of presentation and treatment modality adopted had some bearing on survival. Even though the patients presented at a late stage with high-grade lesions, some patients survived when prompt and effective treatment with wide excision and chemotherapy was carried out. On the other hand, uncontrollable local recurrence occurred within 1 year after primary excision in some grade II patients, who had had surgery and radiotherapy as treatment. Metastases occurred in one each from grade II and grade IV even after having adjuvant chemotherapy as treatment. This points to the fact that prognosis of a lesion cannot be determined by one factor alone.

Discussion

Tumors of the bone are among the most uncommon of all types of neoplasms. Although it is comparatively rare, osteosarcoma is still a common primary bone tumour of the jaws. (Batsakis, 1987). The prevalence of JOS is 10 times greater than that of OS in the total body skeleton, considering that jaws represent only 0.86% of the total body volume (Hoffman *et al*, 1987) and 6.5% of all osteosarcomas. This highlights the importance of understanding the nature of JOS.

Osteosarcoma of the long bones peaks in the second decade (Forteza *et al*, 1986), whereas JOS occurs in an older age group between the third and fourth decade (Garrington *et al*, 1967). According to Garrington, the mean age of JOS ranges from 34 to 36 years. In the present study, lesions occurred over a wide age range with a mean age of 34.1 years. This is inconsistent with the values reported by August *et al* (1997) and Clark *et al* (1983).

The gender distribution of JOS is a controversial issue. Men seem to be more commonly affected. In a review of JOS in the medical literature by Mardinger *et al* (2001), there was a male predilection with a male:female ratio of 1.2:1.0. In line with another study (August *et al*, 1997), we found male predominance with a male:female ratio of 1.1:1.0. This has been attributed to the longer period of skeletal growth and additional volume of bone in men, though neither has been confirmed.

There are reports that JOS shows fairly even distribution between the mandible and the maxilla. In the present study, there was a slight mandibular predilection, in accordance with other studies (Garrington *et al*, 1967; Hoffman *et al*, 1987; August *et al*, 1997). However, higher prevalence in the maxilla was reported by less number of studies (Clark *et al*, 1983).

Although the exact cause of OS is unknown, a number of risk factors have been identified. Rapid bone growth has been regarded as a major predisposing factor (Garrington *et al*, 1967), considering the increased incidence during adolescent growth spurt and the typical location of the tumor near the metaphysial growth plate of the long bones. However, the fact that JOS peaks one or two decades after adolescence may exclude growth as a major etiologic factor. Environmental factors such as ionizing radiation and chromium oxide, a radioactive scanning agent, have also been incriminated (Unni, 1996). Genetic predisposition to OS was observed in patients with mutated P_{53} tumor suppressor gene and mutated retinoblastoma gene. In older patients, OS has been found to occur secondary to benign bone lesions such as Pagets' disease and fibrous dysplasia (Unni, 1996).

The characteristic clinical presentation of OS of long bones is bone pain during activity. In jaw lesions however, pain is not a prominent feature and swelling is the commonest presenting complaint (Garrington *et al*, 1967; Hoffman *et al*, 1987). In the present study, most patients related the occurrence of tumor to previous dental treatments – most commonly, dental extractions. The reason for this is most likely to be the rapid growth of tumor immediately after tooth extraction, a phenomenon often shown by bone tumors (Adekeye *et al*, 1987).

The radiographic appearance of OS varies depending on the inter-relationship between destruction of preexistent cortical or medullary bone, calcification and new bone production and periosteal new bone formation (Unni, 1996). Accordingly, radiographic appearance may be purely osteolytic, osteogenic, or mixed. If the tumor invades the periosteum, many thin irregular spicules of new bone may develop outward and perpendicular to the surface of the lesion producing the so-called 'sun ray appearance.' In an analysis of OS of the mandible, Lindquist *et al* (1986) reported that the widening of periodontal ligament space and inferior dental canal, together with sunburst effect are almost pathognomonic of JOS. The radiographic appearance of OS is suggestive of malignancy, but because of its nonspecific nature it is certainly not a dependable criterion for definitive diagnosis. The importance of special investigations such as computerized tomography (CT) and magnetic resonance imaging lies in assessing the size of the lesion for staging, intramedullary and extramedullary involvement, tumor calcification and invasion into adjacent tissues particularly pterygopalatine fossa, infra temporal fossa and cranial cavity.

This highlights the importance of histopathologic analysis in the diagnosis of osteosarcomas. Histopathologically, OS of long bones and jaw bones share common features. The diagnosis of osteosarcomas is based on the recognition of osteoid production by tumor cells (Schajowicz, 1993). There may be chondroblastic or fibroblastic elements as well. Depending on the predominant type of extracellular matrix present, OS are categorized histopathologically into osteoblastic, chondroblastic, or fibroblastic subtypes (Unni, 1996). It is difficult to differentiate some tumors from malignant fibrous histiocytomas (Ushigome *et al*, 1998).

In our series, OOS was the commonest histopathological variant. In OOS, osteoid is present as lace-like networks between individual tumor cells. The matrix may undergo calcification focally. Most studies state that JOS has higher prevalence of chondroblastic subtype (Garrington *et al*, 1967). In contrast, Bennett *et al* (2000) and Mardinger *et al* (2001) reported considerably lesser prevalence. In the present study, although OOS had the highest prevalence of 53%, COS followed closely with

42%. According to the literature review by Mardinger, COS had the highest prevalence with 42% and OOS closely followed with 33%. These reflect the lack of clear consensus when defining the osteoblastic and chodroblastic variants, as Bennett clearly pointed out. In COS, tumor cells lie in lacunae and form lobules. The center of the lobule has bony trabeculae producing a feathery appearance, and toward the periphery, the tumor becomes hypercellular. FOS, unarguably, is the least common histologic variant of OS. The tumor cells are spindle shaped and arranged characteristically in herring bone pattern. Designation as osteoblastic or chondroblastic variant seems to have a prognostic significance, because the latter reportedly has a better prognosis (Bennett *et al*, 2000). In the present series also COS had less distant metastases and better survival. Osteoblastic, chondroblastic and fibroblastic cells seem to have a common cell lineage. When fibroblastic cells derived from marrow stroma were implanted *in vivo* in diffusion chambers, a bone-like tissue formed peripherally, with chondroblastic and fibroblastic areas centrally (Ashton *et al*, 1980). These observations have suggested that an oxygen or nutrient gradient may help to determine whether a cell will become osteoblastic or chondroblastic.

Histologic diversity of osteosarcomas points to the fact that histology alone is insufficient for the diagnosis of OS. Therefore, combined clinical, radiographic and histopathologic analysis before definitive diagnosis is prudent. Moreover, modern diagnostic aids, such as immunohistochemical studies are being evaluated. A recently found gene encoding an intranuclear osteocalcin promoter – cbfa1 – appears to be a potential marker in the definitive diagnosis of malignant bone tumors (Otto *et al*, 1997). In addition, the detection of alkaline phosphatase activity in imprint preparations obtained from the cut surface of osteosarcoma before fixation is regarded as diagnostic of osteosarcoma, when used in combination with radiographs. A negative result however may not exclude the diagnosis.

Histopathologic grading of OS follows the Broders' grading system developed for epitheliomas, based on the degree of cellular anaplasia shown by tumor cells (Broders, 1925). In agreement with Batsakis (1987), JOS tends to be differentiated better than its long bone counterpart. Mardinger stated that nearly 50% of JOS are low grade and according to Unni, the commenest form is grade II. In the present study also, grade II had the highest prevalence. According to some studies, grade of JOS is important in prognostic evaluation of a tumor, as poorer the differentiation, lesser the chances of survival (Delgado *et al*, 1994; Doval *et al*, 1997). However, according to our experience, some patients with high-grade JOS, who received extensive treatment, survived better than some patients with low-grade malignancy, whose treatment was deferred. According to our study, it seems critical that prompt and correct treatment is needed irrespective of the grade. Therefore, this highlights the fact that grade of malignancy is not the single reliable indicator of the behavior of the tumor.

The so-called 'correct treatment' is not yet clearly understood, although it implies surgical removal with wide margins and adjuvant chemotherapy or radiotherapy as needed. The presence of micro metastases decides the need of adjuvant therapy. This is difficult to assess and therefore all JOS are considered as having micro metastases at the time of presentation, so that any diagnostic errors are overlooked. We believe that the histopathologic type and grade of malignancy alone cannot be used to determine the prognosis of JOS. Staging of tumor according to conventional staging systems used for other solid tumors is not applicable for bone tumors, as OS rarely involve regional lymph nodes. A special staging system devised by Enneking and Kagan (1975), based on the grade, extra medullary spread and metastases, is used for grading of OS.

The treatment of JOS should be approached in two ways. Radical surgery is the primary treatment for OS of long bones as well as jaws, although it cannot be contemplated as the sole treatment (Garrington *et al* 1967; Clark *et al* 1983; Forteza *et al* 1986). Survival is favorable when surgical margins are clear of tumor (Delgado *et al*, 1994). According to August, clear surgical margins correlated statistically with improved survival. In the mandible, hemimandibulectomy is commonly performed. Maxillary lesions are often difficult to be treated as involvement of maxillary sinus, pterygopalatine fossa and orbital fossa often masks the tumor until extensive spread. Often, maxillectomy is inevitable. If cervical lymph nodes are involved, neck dissection would improve the survival (Garrington *et al* 1967). Chemotherapy (CT) has become an important therapeutic adjuvant in the treatment of osteosarcomas of all sites, ever since Jaffe (1972) reported successful results with high dose of methotrexate for the treatment of OS of long bones. Rosen *et al* (1982) reported 93% recurrence-free survival at a median follow-up of 20 months, in long bones, using preoperative and postoperative chemotherapy combined with radical surgery. The most commonly used chemotherapeutic agents are doxorubicin, cisplatin, adriamycin and high-dose methotrexate. Chemotherapy was effective in combating subclinical metastases in OS of long bones and the 5 year survival rate for patients treated with surgery alone was 15%, but this increased to 60–80% for patients treated with surgery and chemotherapy (Rosen *et al*, 1982). The effectiveness of CT for JOS has been a controversial issue, ever since its invention. According to an analysis of 201 reviewed cases of JOS, it was found that the overall and the disease-free survival rates significantly improved with CT (Mardinger *et al*, 2001). This fact was clearly highlighted in our study where the survival rates of patients who had surgery and radiotherapy as treatment was 20% for a median follow-up of 3 years, whereas patients who had surgery and chemotherapy had a survival rate of 83.3% for a median follow-up period of 5.25 years. However, CT in addition to surgery has been applied in many cases with no significant change in prognosis (Mardinger *et al*, 2001). These controversial findings may be due to the diversity of chemotherapeutic regimens used with different agents, dosages, and intervals. Therefore, drawing conclusions about their efficacy have become difficult.

The most often used procedure is Rosen's protocol/ Sandwich technique, which includes preoperative CT, radical surgery, and postoperative CT (Rosen *et al*, 1982). The excisional biopsy will determine the accuracy of excision as well as the response of tumor to preoperative CT, by comparing with the incisional biopsy. This will assist in the selection of the postoperative chemotherapeutic protocol.

Radiotherapy (RT), although commonly used as a main mode of treatment, must be confined for the treatment of residual, recurrent, and unresectable tumors. According to Sibille *et al* (1992), CT has completely substituted radiotherapy. Prophylactic lung radiotherapy has also been given up due to the risks of pulmonary fibrosis entailed by the effective doses. Delgado reported that when surgical margins are not free of disease, radiation does not improve the outcome. However, some report that alone or in combination with surgery, RT has resulted in long-term survival of OS patients (Forteza *et al*, 1986). As most patients are young, reconstruction must be immediate and directed to produce the best possible functional and morphological result (Jaffe, 1972).

Jaw osteosarcomas have better prognosis than conventional osteosarcomas. Clark *et al* (1983) attributed this to the occurrence of predominantly chondroblastic low-grade osteosarcomas in the jaws. For conventional osteosarcomas 5 year survival rate is 20.3%, whereas for JOS it is 40% (Unni, 1996). In our study, for a median follow-up period of 5.25 years the survival rate was 64.2%. The average survival period was 2.25 years. OS spreads microscopically along marrow spaces and inferior dental canal. Extracted tooth sockets may enhance extra-osseous spread. Local recurrence is the commonest complication of JOS (Garrington *et al* 1967; Clark *et al* 1983; Mardinger *et al* 2001). Distant metastases are rare (Garrington). According to our study, recurrences and distant metastases occurred in equal numbers. Uncontrollable local spread is the main cause of death due to JOS. Of the five deaths that were encountered in our patients, two were due to uncontrollable local recurrences and two were due to distant metastases. The cause for one death was unknown.

Conclusions

Osteosarcoma of jaw bones is a group of lesions distinct from the conventional type occurring in long bones, with a better prognosis if diagnosed and treated at an early stage. Uncontrolled local recurrence is the main cause of death. Surgical excision with adjuvant chemotherapy has better survival than with adjuvant radiotherapy, as in the case with osteosarcomas of long bones. Prognosis of JOS mainly depends on clear excision margins, presence or absence of micro metastases and the efficacy of control of micro metastases. Epidemiologic parameters such as age, gender, and site do not show any characteristic relationship to its prognosis. Although COS is attributed to better prognosis, histological type is not a main determinant of prognosis. Histologic grade alone may not be a reliable indicator in determining prognosis.

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