

Gnathic Osteosarcomas- An Institutional Experience Of 10 Cases

Philip John Kottaram , Deepak Janardhan, ,Shaji Thomas,
Nebu Abraham George, Bipin T Varghese
Department of Surgical Oncology, Regional Cancer Centre , Trivandrum, Kerala

Abstract

Background: Sarcomas are neoplasms arising from the mesodermal tissue and constitute < 1% of body tumors. Of these, only 5-15% occur in the head and neck region. Among these osteosarcomas are the most common. They are difficult to treat due to their aggressiveness, propensity for recurrence and their proximity to vital anatomical structures. There is no general consensus on the adjuvant modality of management.

Methods: 10 patients with head and neck osteosarcoma, surgically treated at our institute from 2000 to 2016 were reviewed retrospectively.

Results: Mandible was the most common affected site followed by maxilla. The disease had a male preponderance. Chondroblast type was the most common histopathological variant in our study group. A multimodality treatment approach was used comprising of neoadjuvant chemotherapy followed by surgery, with or without post op radiotherapy and chemotherapy in the patients. After a median follow-up of 1 yr, around 38 % were alive and disease free. Postoperative adjuvant radiotherapy for local control failed to attain statistical significance.

Conclusions: Surgery is the mainstay of the treatment of head and neck osteosarcoma. Adjuvant therapy, however, has doubtful benefit.

Keywords: Craniofacial osteogenic sarcoma, Gnathic tumours, Osteosarcoma, Jaw tumours

I. Introduction

Osteosarcoma of the Jaws, are rare entities unlike the corresponding ones involving the extremities. The differences not only lie in the clinicopathological aspects but in the treatment and survival aspects as well. The anatomical constraints in the craniofacial areas limit the wide resection requirement to treat such case scenarios. However, there is wide variation in the projected survival of such patients in the literature, probably due to the limited number of cases and varying adjuvant treatment schedules practiced worldwide. The aim of the study was to assess the clinicopathological behaviour, recurrence pattern and survival in surgically treated Gnathic Osteosarcomas with or without adjuvant treatment at our institution.

II. Materials And Methods

A Retrospective study of all surgically treated and regularly followed up patients with osteosarcomas of the jaw at our institution from January 2000-January 2015 was done. Demographic profile, treatment given and outcome were analysed. Statistical analysis was done with SPSS 15.

III. Results

A total of 10 patients were included in the study who were surgically treated in our institute from January 2000 to 2015. Of the analysed patients 6 were men and 4 were women. The age range was fairly distributed with 40% belonging to 21-40 yrs age group and 30% belonging to the 41-60yr age group. Mandible was found to be the most common subsite (60%) followed by maxilla (40%) (Fig-1). The median follow up period was 19 months. None of the 10 patients had a prior history of any proven malignancy or any prior radiation exposure. Chondroblastic type was the most common histologic subtype (60%) followed by osteoblastic (30%) and a mixed subtype in 10% of the patients. Most of the patients presented with a painless swelling over the maxilla or mandible. 50% of the patients had evidence of nodal involvement during evaluation. None of the patients had any sign of distant metastasis at the time of presentation. All the patients received multimodality treatment consisting of surgical resection, neoadjuvant chemotherapy & radiotherapy. All the patients were treated with radical intent. All the patients underwent surgical resection of varying extent. A complete surgical resection (R0) was attained in 60% cases, Gross total resection (R1) in 30% patients and incomplete excision in 10% Patients. Neoadjuvant and post-operative chemotherapy was offered for 80% of the patients under study. The chemotherapeutic protocols involved usage of a combination of Doxorubicin, Cisplatin and Ifosfamide. Patients with close or positive margins received or with extensive soft tissue involvement received post operative adjuvant radiotherapy and those with local recurrence or distant metastasis received palliative radiation. 70% of the patients received adjuvant radiotherapy.

Though, the first year overall survival was noted to be 90% ,it dropped to 38.6% for second year after treatment (Figure -2).The overall survival probability by age group was 75% for those within the age group of 21-40yrs and 66.7 % for those within the age group of 41-60yrs within the first 1 yr. The probability of relapse free survival in first year of post treatment was 44%.The relapse free survival probability in the first 1 yr by age group was 33.33 % in the age group between 21-20yrs and 66.7% in 41-60yrs age group. The overall survival probability was higher in males (83.3%) when compared with Females (66.7%). But the relapse free survival was more in Females (50%) when compared with males (40%) within the first treatment year.

People whose primary site of involvement was mandible had a higher survival probability of 83.3% when compared to those whose had primary involvement of maxilla (66.7%).Though various parameters like age, gender, surgical margin status, adjuvant therapy were analysed for survival, no statistical significance was noted between the parameters analysed.

Demographic And Clinicopathological Data			Overall Survival Probability 1 st year	P	Relapse Free Survival 1 st year	P
Gender	Male	6	83.3.5%	0.264	40%	0.792
	Female	4	66.7%		50%	
Site	Maxilla		66.7%	0.859	25%	0.109
	Mandible		83.3%		60%	
Extent of Resection	Complete Resection with Clear Margin (R0)	6	84%	0.354	40%	0.130
	Gross Total Resection (R1)	4	66%		23%	
Adjuvant Therapy	Neoadjuvant Chemotherapy	8	62%	0.265	43.7%	0.389
	Radiotherapy	7	67%		66.7%	

Figure-1. Clinicopathological and demographic data showing first year over all and relapse free survival with respect to various variables and their significance.

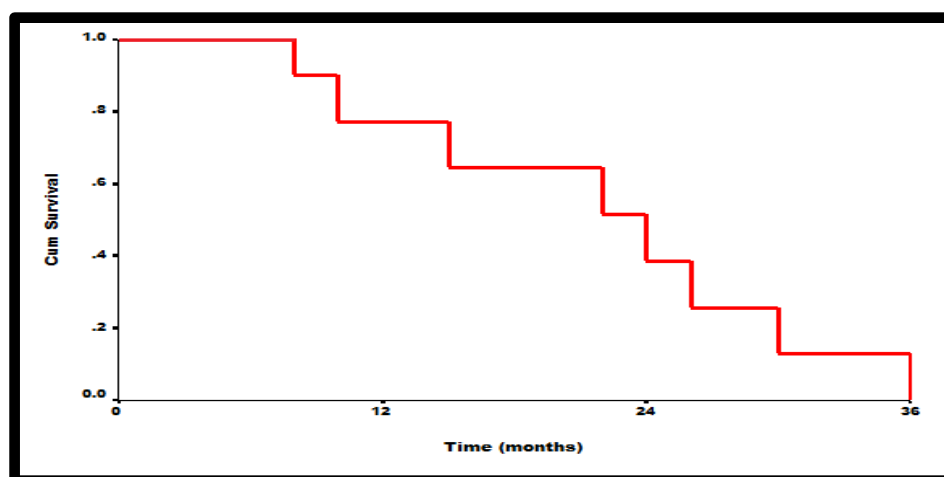


Figure -2 Kaplan Meier Survival analysis showing 1st yr Overall Survival Probability of 90%, that drastically falls in 2nd yr to 38.6%.

IV. Discussion

Gnathic or Craniofacial osteosarcomas are rare, but clinicopathologically distinct group of lesions, unlike, the conventional ones affecting extremities. OS though account for 15% of all primary bone tumors and 1% of all head and neck malignancies [1]., Jaw osteosarcomas represent only 5–13% [2] of them.[3].They arise from undifferentiated mesenchymal cells that transform into bone or osteoid tissue [4] Gnathic osteosarcomas can be either primary with unknown etiology or secondary[5] to skeletal Paget's disease,[6] fibrous dysplasia of bone or as a late sequela to craniofacial irradiation.[7,8] Osteosarcoma of the jaws usually present at the third or fourth decade of life [1]as in our study most of the patients were within the age group of 21-40 yrs; that is older than the corresponding osteosarcomas of extremities. Histologically , osteosarcomas of the jaws are better

differentiated than their long bone counterparts as majority show cartilaginous differentiation [12]. They have lower incidence of metastasis [3,9], unless postradiated [10]. A 5-year survival rate of 40% for jaw osteosarcomas compared to 20.3% for conventional osteosarcomas have been reported [11,12]. However in our study the overall survival probability dropped drastically from 90% to 38.8% by the second year of radical treatment. This can most likely be attributed to the higher stage of initial presentation and the aggressive nature of the disease. Clark et al [13] attributed this to the commoner, chondroblastic low grade osteosarcomas in the jaws. But, local recurrences are commoner [14,15,16] and difficult to control, leading to death of the patients. [17]

Gnathic Osteosarcomas have predilection for posterior portion of the alveolar process and the antrum in maxilla. Correspondingly, body is most commonly involved in the mandible followed by angle, symphysis, and ascending ramus. Slightly higher incidence in males have been reported [18,19] as noted in our series where 60% were males, probably due to the longer period of skeletal growth and additional volume of bone in men. Maxillary osteosarcomas are commoner in females with the ratio of 4:1 whereas mandibular lesions are commoner in males [17]. As, jaw osteosarcomas peak one or two decades after adolescence, rapid bone growth cannot be attributed as etiological factor. Mostly, environmental factors such as ionizing radiation have a causative role. Swelling rather than pain is the commonest presentation. [3,21] Paraesthesia or numbness due to inferior alveolar nerve infiltration has been reported and it implies poor prognosis.

Locoregionally, Osteosarcomas can spread microscopically through recently extracted tooth socket, the mandibular canal, the periodontal ligament, the mental nerve, the inferior alveolar nerve, or destroying the cortex [22]. Distant Metastasis is usually via the bloodstream with most common site being lung. 20% of all patients with osteosarcoma have lung metastases at diagnosis. In our group of patients, suspicious nodule in lung was noted in 40%. Most of them were indeterminate in nature. This is usually difficult to distinguish within our patient subgroups due to higher incidence of tuberculosis and other infective lung pathologies. Prognosis is comparatively favorable when unilateral and or when with fewer pulmonary nodules. However the rate of micrometastases is estimated to be 80% [1].

Imageologically, widening of periodontal ligament [23] space is considered pathognomonic of osteosarcoma of jaw bone. Presence of destructive unicentric lesion with sclerotic, lytic or mixed radiographic pattern is suggested to be suspicious of osteogenic sarcoma [17]. Histological characteristic is presence of osteoid. [24]. Depending upon the predominant type of extracellular matrix, osteosarcomas are divided, histopathologically, into chondroblastic (43%) [2], osteoblastic and fibroblastic subtypes. [25]. Pleomorphism, cellular atypia, mitotic figures and necrosis are correlated while grading. Wide radical resection is the treatment of choice for osteosarcoma of jaws [20,26] with clearance margins of 1.5–2 cm. Adjuvant chemotherapy and or radiotherapy is recommended in view of micro metastases, and close margins due to anatomical constraints. Radiotherapy alone is offered for unresectable residual or recurrent tumors. Age wise, older patients are reported to have increased resistance to the tumor and so better prognosis. Site wise, a better 5-year-survival rate of 34.8 percent for the mandible against 25.8 percent for the maxilla has been reported [3,27]. The median survival time for the maxilla is 2.9 years and 6.5 years for the mandible [28]. This correlated with our study as patients who had primary involvement of the mandible had a higher survival probability of 83.3%. However chances of local failure is around 33% to 39% [18].

Literature search revealed contradicting survival benefits with adjuvant treatment. The 5-year survival for patients treated with adjuvant chemotherapy is 33% and for those treated with surgery alone is 41% [29]. Surgery followed by radiation or chemoradiation is reported to have better survival by some authorities [30,31,32]. In our study, the use of an adjuvant treatment could not demonstrate a statistical difference in survival within the treatment groups. However, the degree of necrosis in the primary tumor after induction chemotherapy remains prognostic in metastatic osteosarcoma. Early distant metastases have been reported in approximately 50% of the cases at diagnosis. Multifocality and skip metastasis are associated with poor prognosis. [33-38]

V. Conclusion

Rarity of this, clinico-radiologically heterogeneous entity in a constrained anatomy limiting adequate surgical clearance and diversity in the existing adjuvant and or neoadjuvant treatment schedule is the probable cause hindering the development of ideal universal treatment strategies for Gnathic Osteosarcomas. However existing practice still remains to be wide surgical excision with clear margins and adjuvant chemoradiation for the best possible prognosis.

Despite, it still remains to be aggressive with high rate of mortality and low disease free survival. Our study doesn't show usage of adjuvant treatment to be significantly altering the outcome.

References

- [1]. Thiele OC, Freier K, Bacon C, Egerer G, Hofele CM. Interdisciplinary combined treatment of craniofacial osteosarcoma with neoadjuvant and adjuvant chemotherapy and excision of the tumour: a retrospective study. *Br J Oral Maxillofac Surg.* 2008;46(7):533–536.
- [2]. Mardinger O, Givol N, Talmi 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
- [3]. Garrington GE, Scofield HH, Cornyn J, Hooker SP. Osteosarcoma of jaws, analysis of 56 cases. *Cancer.* 1967;20:377–91.
- [4]. J. H. Bennett, G. Thomas, A. W. Evans, and P. M. Speight, “Osteosarcoma of the jaws: a 30-year retrospective review,” *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, vol. 90, no. 3, pp. 323–333, 2000. View
- [5]. Rajendran R. Benign and Malignant tumors of the oral cavity. In: Rajendran R, Sivapathasundharam B, editors. *Shafer's textbook of Oral Pathology*. India: Elsevier, a Division of Reed Elsevier India Private Limited; 2006. pp. 113–308.
- [6]. Brackenridge CJ. A statistical study of sarcoma complicating Paget's disease of bone in three countries. *Br J Cancer.* 1979;40:194–200.
- [7]. Huvos AG, Woodard HQ, Cahan WG, Higinbotham NL, Stewart FW, Butler A, et al. Postradiation osteogenic sarcoma of bone and soft tissues. A pathological study of 66 patients. *Cancer.* 1985;55:1244–55.
- [8]. D. S. Vege, A. M. Borges, K. Aggrawal, G. Balasubramaniam, D. M. Parikh, and B. Bhaser, “Osteosarcoma of the craniofacial bones. A clinico-pathological study,” *Journal of Cranio-Maxillo-Facial Surgery*, vol. 19, no. 2, pp. 90–93, 1991
- [9]. M. S. Weinfeld and H. R. Dudley Jr., “Osteogenic sarcoma. A follow-up study of the ninety-four cases observed at the Massachusetts General Hospital from 1920 to 1960,” *Journal of Bone and Joint Surgery*, vol. 44, pp. 269–276, 1962.
- [10]. J. J. Kasthoori and M. L. Wastie, “Radiation-induced osteosarcoma of the maxilla,” *Singapore Medical Journal*, vol. 47, no. 10, pp. 907–909, 2006.
- [11]. Unni KK, Dahlin DC. Grading of bone tumors. *SeminDiagPathol.* 1984;1:165–72.
- [12]. Nissanka EH, Amartunge EA, Tilakaratne WM. Clinicopathological analysis of osteosarcoma of jaw bones. *Oral Dis.* 2007;13:82–7.
- [13]. Clark JL, Unni KK, Dahlin DC, Devine KD. Osteosarcoma of the jaw. *Cancer.* 1983;51:2311–6.
- [14]. Diniz AF, Filho JA, Alencar Rde C, Garcia RR, Silva MR, Ribeiro-Rotta RF, Silva MA, Batista AC, Mendonça EF. Low-grade central osteosarcoma of the mandible: a case study report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103(2):246–252.
- [15]. Zhao W, Cure J, Castro CY. Low-grade osteosarcoma of the jaw. *Ann Diagn Pathol.* 2002;6(6):373–377.
- [16]. Bertoni F, Bacchini P, Fabbri N, Mercuri M, Picci P, Ruggieri P, Campanacci M. Osteosarcoma. Low-grade intraosseous-type osteosarcoma, histologically resembling parosteal osteosarcoma, fibrous dysplasia, and desmoplastic fibroma. *Cancer.* 1993;71(2):338–345.
- [17]. Forteza G, Colmenero B, Lopez-Barea F. Osteogenic sarcoma of maxilla and mandible. *Oral Surg Oral Med Oral Pathol.* 1986;62:179–84.
- [18]. August M, Magennis P, Dewitt D. Osteogenic sarcoma of the jaws: Factors influencing prognosis. *Int J Oral Maxillofac Surg.* 1997;26:198–204.
- [19]. Staging of musculoskeletal neoplasms. *Musculoskeletal Tumor Society. Skeletal Radiol.* 1985;13:183–94
- [20]. Angiero F, Moltrasio F, Cattoretti G, Valente MG. Clinical and histopathological profiles of primary or secondary osteosarcoma of the jaws. *Anticancer Research.* 2011;31(12):4485–89.
- [21]. Hoffman S, Jakoway JR, Krolls SO. Intraosseous and Parosteal tumors of jaws. *Atlas of tumor pathology*. Washington, D.C: AFIP; 1987. Malignant odontogenic tumors of jaws; pp. 170–80.
- [22]. Petrikowski GC, Pharoahi MJ, Lee L, Grace MGA. Radiographic differentiation of osteogenic sarcoma, osteomyelitis and fibrous dysplasia of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1995;80:744–50.
- [23]. Lindquist C, Teppo L, Sane J, Holmstrom T, Wolf J. Osteosarcoma of mandible: Analysis of 9 cases. *J Oral Maxillofac Surg.* 1986;44:759–64.
- [24]. Schajowicz F. 2nd ed. Berlin: Springer-Verlag; 1993. Histological typing of bone tumours.
- [25]. Frei C, Bornstein MM, Stauffer E, Iizuka T, Buser D. Osteosarcoma of the maxilla and the maxillary sinus: A case report. *Quintessence Int.* 2004;35:228–33.
- [26]. Hu X, Yu AX, Qi BW, Fu T, Wu G, Zhou M, et al. The expression and significance of IDH1 and p53 in osteosarcoma. *J Exp Clin Cancer Res.* 2010;29:43.
- [27]. P. J. Slootweg and H. Muller, “Osteosarcoma of the jaw bones. Analysis of 18 cases,” *Journal of Maxillofacial Surgery*, vol. 13, no. 4, pp. 158–166, 1985.
- [28]. G. Patel, P. Meyers, A. G. Huvos et al., “Improved outcomes in patients with osteogenic sarcoma of the head and neck,” *Cancer*, vol. 95, no. 7, pp. 1495–1503, 2002.
- [29]. Raymond AK, Spires J, Ayala A, Chawla S, Lee YY, Benjamin RS, et al. Osteosarcoma of head and neck. *Lab Invest.* 1989;60:76a.
- [30]. Guadagnolo BA, Zagars GK, Raymond AK, Benjamin RS, Sturgis EM. Osteosarcoma of the jaw/craniofacial region: outcomes after multimodality treatment. *Cancer.* 2009 Jul 15;115(14):3262–70.
- [31]. Chindia ML. Osteosarcoma of the jaw bones. *Oral oncology.* 2001;37(7):545–47.
- [32]. Demicco EG, Deshpande V, Nielsen GP, Kattapuram SV, Rosenberg AE. Well-differentiated osteosarcoma of the jaw bones: A clinicopathologic study of 15 cases. *American J Surgical Pathology.* 2010;34(11):1647–55.
- [33]. Kaste SC, Pratt CB, Cain AM, Jones-Wallace DJ, Rao BN. Metastases detected at the time of diagnosis of primary pediatric extremity osteosarcoma at diagnosis: imaging features. *Cancer.* 1999;86:1602–8.
- [34]. Bacci G, Briccoli A, Ferrari S, Saeter G, Donati D, Longhi A, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with synchronous lung metastases: treatment with cisplatin, adriamycin and high dose of methotrexate and ifosfamide. *Oncol Rep.* 2000;7:339–46.
- [35]. Bacci G, Briccoli A, Ferrari S, Longhi A, Mercuri M, Capanna R, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremity: long-term results of the Rizzoli's 4th protocol. *Eur J Cancer.* 2001;37:2030–9.
- [36]. Bacci G, Briccoli A, Mercuri M, Ferrari S, Bertoni F, Gasbarrini A, et al. Osteosarcoma of the extremities with synchronous lung metastases: long-term results in 44 patients treated with neoadjuvant chemotherapy. *J Chemother.* 1998;10:69–76.
- [37]. Sajadi KR, Heck RK, Neel MD, Rao BN, Daw N, Rodriguez-Galindo C, et al. The incidence and prognosis of osteosarcoma skip metastases. *Clin Orthop Relat Res.* 2004;426:92–6.
- [38]. Longhi A, Fabbri N, Donati D, Capanna R, Briccoli A, Biagini R, et al. Neoadjuvant chemotherapy for patients with synchronous multifocal osteosarcoma: results in eleven cases. *J Chemother.* 2001;13:324–30.