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Radical Surgical Treatment in Craniofacial Osteosarcoma Gives Excellent Survival. A Retrospective Cohort Study of 14 Patients

L.E. Smeele, J.E. van der Wal, P.J. van Diest, I. van der Waal and G.B. Snow

14 patients with an osteosarcoma of the craniofacial bones were evaluated retrospectively. 10 patients were males and 4 were females, ages varied from 10 to 74 years with a mean of 37 years. Ten tumours were located in the maxilla and four in the mandible. All patients underwent surgical resection of the tumour. One patient was irradiated postoperatively with 67.5 Gy and another patient received adjuvant chemotherapy with melphelan. Follow-up ranged from 6 months to 10 years with a mean of 4 years 2 months. Of 14 patients, 5 have died of local disease of whom 1 also had distant metastasis. Disease-free survival was 82.5% after 2 years and 68.8% after 5 years. Overall survival was 79.1% after 5 years. Univariate statistical analysis was carried out, revealing age <35 years ($P=0.033$) and radical surgery ($P=0.007$) as statistically significant factors in disease-free survival. It is concluded that radical surgery in young patients with a craniofacial osteosarcoma gives long-term disease-free survival.

Keywords: facial bones, jaw diseases, osteosarcoma, skull, surgery, survival

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INTRODUCTION

OSTEOSARCOMA (OS) is a relatively rare, but highly malignant disease. Annual incidence ranges from 1.2 to 3.3 per million [1]. In OS of the long bones, 5-year survival has been as low as 5–10% with surgical therapy alone with patients generally dying from pulmonary metastasis. Due to the introduction of adjuvant chemotherapy, survival has increased considerably [2]. At present, there is some evidence that further gain can be expected from neoadjuvant protocols as well as from additional surgery for pulmonary metastasis in selected patients [3, 4].

Craniofacial OS comprises up to 6.0–8.8% of all primary OS [1, 5]. Traditionally, treatment of craniofacial OS consists of surgery. In this retrospective cohort study, disease-free survival of craniofacial OS is evaluated with reference to the effect of primary surgery.

PATIENTS AND METHODS

During the years 1969–1993, 14 patients were registered at the Departments of Oral and Maxillofacial Surgery, Oral Pathology and Otolaryngology and Head and Neck Surgery with a diagnosis of OS. Follow-up ranged from 6 months to 10 years, mean 4 years 2 months. The patient's records and original histological slides were reviewed as well as their plain radiographs, tomographs and computed tomographs.

10 patients were male and 4 female, ages ranged from 10 to 74 years at time of referral, mean 37 years (Fig. 1). Patients' characteristics at the time of presentation are summarised in Table 1. In all patients, the definitive diagnosis of OS was based on plain radiography and incisional biopsy. In 10 patients, computed tomography was performed. Mandibular tumours (4 patients) could be distinguished from maxillary ones (10 patients) without difficulty. Among large maxillary

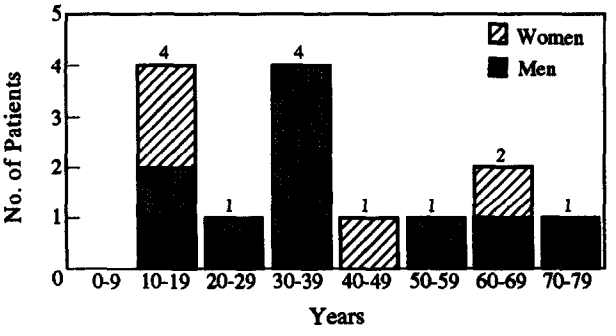

Fig. 1. Age and sex in 14 patients with craniofacial osteosarcoma.

Correspondence to L.E. Smeele.
L.E. Smeele, J.E. van der Wal and I. van der Waal are at the Department of Oral and Maxillofacial Surgery and Oral Pathology; P.J. van Diest is at the Department of Pathology; and G.B. Snow is at the Department of Otolaryngology and Head and Neck Surgery, Free University Hospital, PO Box 7057, NL-1007 MB, Amsterdam, The Netherlands.
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Table 1. Symptoms and initial diagnosis at time of referral in 14 patients with craniofacial osteosarcoma

Symptoms	No. of patients	Initial diagnosis	No. of patients
Swelling	11	Osteosarcoma	5
Pain	4	Chondrosarcoma	4
Loose teeth	2	Fibrosarcoma	1
Dysesthesia	2	Epulis	1
		Periapical disease	1
		Fibrous dysplasia	1
		Not specified	1

Range of duration of symptoms, 1–14 months, mean 4 months.

Table 2. Surgical treatment of 14 patients with craniofacial osteosarcoma

Surgery	No. of patients
Subtotal maxillectomy	7
Total maxillectomy	2
Total maxillectomy with orbital exenteration	1
Hemimandibulectomy	1
Hemimandibulectomy with lymph node dissection	1
Segmental mandibulectomy	1
Marginal mandibulotomy	1

tumours it was sometimes impossible to decide if these were perhaps antral, nasal or ethmoidal tumours. For this reason 'craniofacial' seems to be a more appropriate term.

Four tumours were T1 and 10 were T2 [6]. 4 patients had another tumour. Metachronously, one OS, initially diagnosed as fibrous dyplasia, a fibrosarcoma and an abdominal B-cell Burkitt-type lymphoma Memphis stage III were found. A non-Hodgkin lymphoma stage IA of the axilla was found as a synchronous tumour.

All patients were treated surgically (Table 2). One patient was irradiated postoperatively with a total dose of 67.5 Gy. One patient received adjuvant chemotherapy (melphelan) in a postoperative protocol.

Disease-free interval was defined as the time elapsing from the moment of surgery until either local recurrence or distant metastasis. Overall survival time was measured from initial diagnosis until death or end of follow-up. Statistical analysis was carried out with the Biomedical Package (BMDP, Los Angeles, California, U.S.A.), regarding P-values below 0.05 as statistically significant. Kaplan–Meier curves were plotted and differences between curves were analysed with the Mantel–Cox statistic. Regarding disease-free interval, univariate analysis was carried out. The following variables were defined: age (<35 and $\geqslant 35$ years), sex (male and female), tumour site (mandible and maxilla), multiple tumours (one and two tumours), radical surgery (free surgical margins at the histopathological level), T-stage (T1 and T2 tumours [6]), grade (well and poorly differentiated tumours) and mitotic index (<5 and $\geqslant 5$ mitoses counted in 10 high power fields).

RESULTS

Disease-free survival was 82.5% after 2 years and 68.8% after 5 years. 5 patients have died. One patient died of

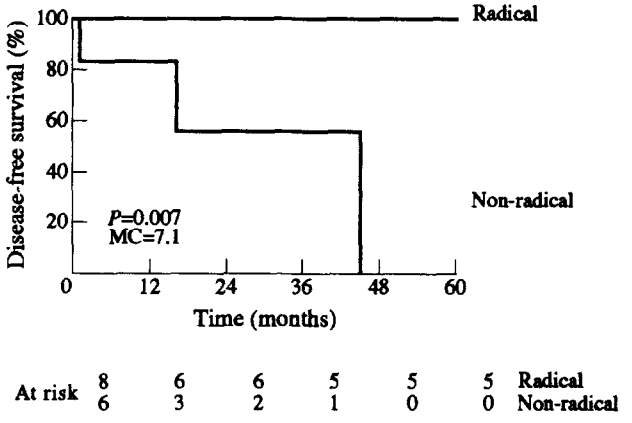

Fig. 2. Recurrence-free interval of 14 patients with craniofacial osteosarcoma who underwent a radical and a non-radical operation.

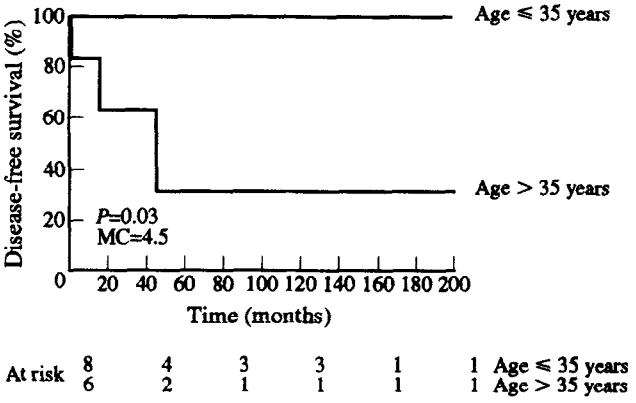

Fig. 3. Recurrence-free interval of 14 patients with craniofacial osteosarcoma with age <35 and $\geqslant 35$ years.

intercurrent and local disease 1 month postoperatively, 3 patients died of local disease and 1 patient died of local disease and distant metastasis. All 5 patients who died and 1 surviving patient, the latter being irradiated postoperatively, had undergone a histologically-proven non-radical operation. Overall survival was 79.1% after 5 years. At univariate analysis regarding disease-free survival, radical surgery ($P=0.007$) and age <35 years ($P=0.033$) were statistically significant factors (Figs 2, 3). Statistically not significant, but possibly indicating a trend were mandibular tumours ($P=0.173$), no second tumour ($P=150$), $<$five mitoses/10 HPF ($P=0.141$) and well-differentiated tumours ($P=0.134$).

DISCUSSION

In the present series of OS, disease-free survival was measured to be 82.5% after 2 years and 68.8% after 5 years. Overall survival was 79.1% after 5 years. It should be noted that only 1 patient died from local and metastatic disease. All other deaths occurred due to local disease after a non-radical resection. At analysis, radical surgery as defined by free surgical margins proved to be a highly significant factor in disease-free survival. These results are favourable compared to other reports on craniofacial OS and far more favourable compared to OS of the long bones.

Patients' characteristics in this series of craniofacial OS

more or less resemble previous reports. Mean age agrees with others' experiences, but it should be noted that variance is considerable (37 and 10–74 years, respectively). It has often been stated that patients with craniofacial OS are older than patients with other skeletal localisations of primary OS. The work of Garrington is often used as a point of reference for this statement [7]. One should realise, however, that this research was carried out in the 1960s, being based on even older data. At present, there is some evidence that the overall age of patients with OS is increasing [1]. We found, that age younger than 35 years is a statistically significant factor in disease-free survival. Whether this is of clinical relevance is doubtful, as the younger age group in our series presented with smaller tumours and all of them underwent a radical operation. In mandibular tumours diagnosis was delayed considerably due to mimicking dental disease, as has also been demonstrated by Lindquist *et al.* [8]. As has been stated before, a definitive diagnosis was made by plain radiography and an incisional biopsy. Computed tomography had no additional diagnostic value, but was helpful in planning surgical margins [9]. Regarding site, we found a maxillary predominance, which is in contrast with some reports [10–12], but resembles others' findings [13].

In this series of OS, there were 4 patients with another tumour. Within this specific group, one OS was possibly radiation-induced due to treatment of a fibrosarcoma, one was interpreted to be a late recurrence and two were second primary tumours. Radiation-induced malignancy is a rare but well-established late complication of radiation therapy. Radiation-induced OS has been reported in the literature previously and the patient in this series matches the general picture well. In a report of 1200 OS from Memorial Sloan-Kettering Hospital, 66 (5.5%) arose as a direct consequence of radiation. Of these, 42 originated in previously normal bone. At the time of diagnosis of the OS, mean age in this group was 40.3 years and a mean time of 12.5 years (range 4–30) had elapsed since the radiation [14].

Second primary tumours are known to occur after non-Hodgkin's lymphoma (NHL) [15]. Among a group of 29 153 survivors of NHL there was a significantly increased risk of developing a second malignancy, proportional with the length of survival. However, this relationship could not be established for bone tumours in non-irradiated patients [16]. In contrast, the Late Effects Study Group has reported recently on secondary malignant neoplasms after a malignancy during childhood. It was found that 22 OS arose secondarily in previously non-radiated bone, of which one arose in the mandible and 21 in the long bones. However, there were no patients with NHL in this group. Regarding chemotherapy, it is concluded that anthracycline significantly shortens the interval to the secondary tumour [17]. The patient in our series with the Burkitt lymphoma had been treated with doxorubicin, but at present it remains unclear as to whether this has contributed to his secondary tumour.

The rate of metastasis in craniofacial OS varies, percentages ranging from 12.5 to 40.0% [10–12, 18]. In the present series, only 1 patient (7.1%) developed distant metastasis. In OS of the long bones, pre-operative (adjuvant) chemotherapy has proven its value with reference to limb-sparing surgery and an acceptable local recurrence rate. It has less impact on distant metastasis [4]. Analogously to treatment of OS of the long bones, there has been some debate as to whether patients with craniofacial OS should be treated with adjuvant chemotherapy. However, there is no evidence from controlled trials on this subject [11, 17].

Based on our experience we conclude that by radical surgery local tumour control and disease-free survival are achieved. Pre-operative chemotherapy may play a role, if a non-radical operation is to be planned. However, the possible value of this has not been proven yet for craniofacial OS. As the development of distant metastasis is a relatively rare event, this is not an indication for chemotherapy. Also, a positive effect of chemotherapy on the occurrence of distant metastasis has not been proven yet.

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