A Clinical Investigation of Oral Sarcomas at Multi-institutions Over the Past 30 Years

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Abstract. *Background/Aim: Sarcoma of the oral cavity is rare accounting for around 1% of all malignant oral tumors. The purpose of this study was to find important prognostic factors for patients with oral sarcoma. Patients and Methods: The study included 1,643 patients examined from April 1980 to March 2010 at the Departments of oral and maxillofacial surgery at multi-institutions who had a histopathological diagnosis of malignant oral tumors. Results: Sarcoma accounted for 19 of 1,643 cases (1.16%) in malignant oral tumors. Histologically, osteosarcoma was most common in 6 of the 19 patients, followed by 3 cases each of leiomyosarcoma and malignant fibrous histiocytoma, 2 of rhabdomyosarcoma and 1 each of angiosarcoma, Ewing's sarcoma, malignant schwannoma, malignant rhabdoid tumor and undifferentiated sarcoma. Irrespective of the histological type, tumor diameter on initial examination was >50 mm in 8 patients, 7 of whom died. Tumor diameter was <50 mm in 11 patients, 6 of whom survived. Distant metastasis was present in 11 patients, 10 of whom died. The local control rate was 42.1% and 5-year survival rate was 36.8%. Conclusion: Treatment of patients with tumors over 50-mm long in diameter and distant metastasis is extremely difficult. The incidence of oral sarcoma is very low. However, tumor diameter and presence of distant metastasis are important prognostic factors for oral sarcoma according to this multi-institutional study.*

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Sarcoma of the oral region is rare accounting for around 1% of all malignant oral tumors (1). Although treatment may be difficult for some histological types of sarcoma, for which no standard therapy has yet been established, we clinically investigated patients with oral sarcoma treated at 3 institutions over the past 30 years. For other histological types, such as osteosarcoma, chemotherapy has come to play an important role and rapid advances in treatment methods have been recently seen (2). However, other groups reported that it was a great challenge to manage oral sarcomas because of their heterogeneous group of tumors of different histological variants (3).

Herein, we report on findings of a clinical investigation of patients with oral sarcoma treated over the past 30 years at 3 institutions, namely, Ehime, Kochi and Yamaguchi University Hospital.

Patients and Methods

This study included 1,643 patients examined between April 1980 and March 2010 at the Departments of oral and maxillofacial surgery of Ehime University, Kochi University and Yamaguchi University and had a histopathological diagnosis of malignant oral tumor. We identified the cases of sarcoma and subjected them to clinical investigation, including the proportion of all malignant tumors; patients' age and sex; primary site, size and histological type of tumor; treatment method; presence of recurrence and distant metastasis; and prognosis. All cases were over 5 years after the treatment. Therefore, 5-year overall survival rate and other various parameters were statistically analyzed by the Wilcoxon signed-rank test. The clinical stage, tumor size and distant metastasis were also analyzed. In this survey, patients with hematological malignancies were excluded and, as the number of induced lesions among patients with rheumatism increased, even patients with malignant lymphoma were excluded as well.

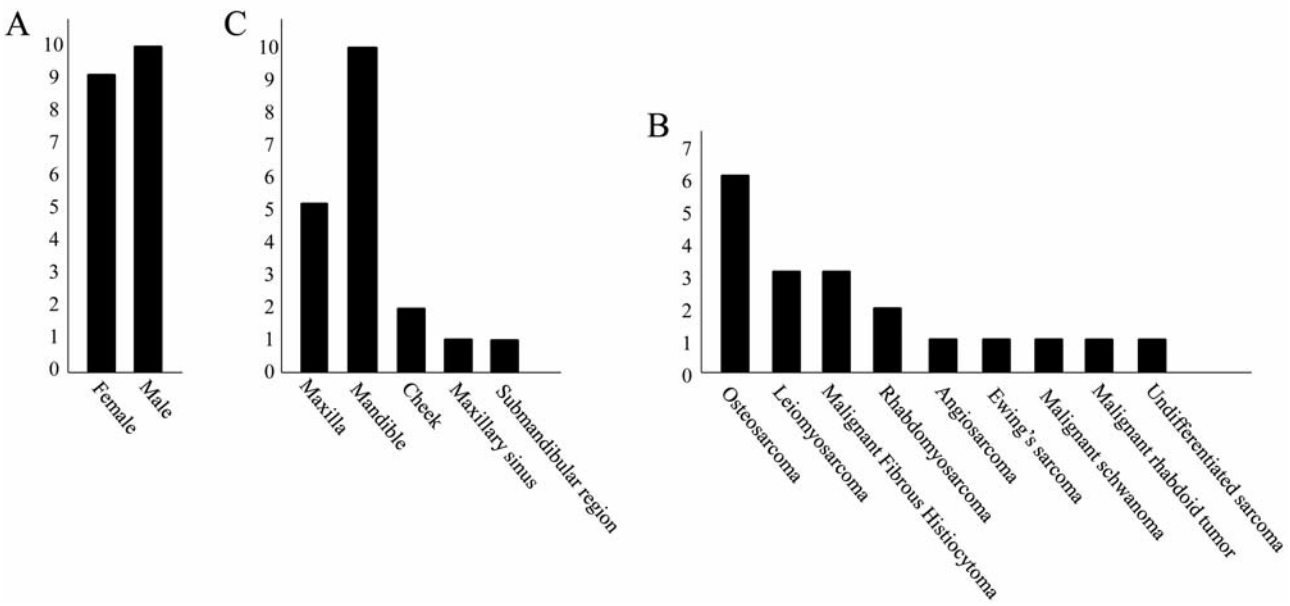

Figure 1. *A: Nineteen patients in total were diagnosed as sarcoma (9 females and 10 males). B: The distribution of histological types. C: The primary site of the sarcoma.*

Results

Sarcoma was present in 19 (9 females and 10 males) of the 1,643 patients (1.16%) with malignant tumor (Figure 1A); the average patient age was 51.2 years (range=17-80).

Histologically, osteosarcoma was most common in 6 (all of them were below 80 mm diameter) of the 19 patients, followed by 3 cases each of leiomyosarcoma and malignant fibrous histiocytoma, 2 of rhabdomyosarcoma and 1 each of angiosarcoma, Ewing's sarcoma, malignant schwannoma, malignant rhabdoid tumor and undifferentiated sarcoma (Figure 1B). The mandible was the most common site of tumor origin, seen in 10 cases, followed by the maxilla in 5 cases reflecting the high proportion of osteosarcoma; the other sites included the cheeks in 2 cases, the maxillary sinus in 1 and the submandibular region in 1 (Figure 1C). Treatment comprised of surgical resection alone in 5 cases, surgical resection with adjuvant chemotherapy in 4 and triple-combination therapy, including radiation in 8. In addition, 2 patients with no hope of curative treatment underwent palliative chemoradiotherapy. Three out of 19 cases showed obvious metastases at the time of initial diagnosis by computed tomography (CT) examination. Therefore, 3 out of 11 cases had primary metastasis. All 19 cases are summarized in Table I.

Table II shows treatment outcomes by cancer stage. This staging was based on the Union for International Cancer Control (UICC) classification on soft tissue and bone and there were no Stage III patients in this study. Although Stages I and II have relatively better prognosis, it was extremely poor in patients with larger-diameter tumors, particularly those of >50 mm, and those with distant metastasis. Tumor diameter on initial examination was >50 mm in 8 patients, 7 of whom died, and <50 mm in 11 patients, 6 of whom survived (Figure 2A). There was a significant difference among these 2 groups ($p<0.05$). Distant metastasis was observed in 11 patients, 10 of whom died, and 8 patients with no metastasis, 6 of whom are alive. There was also a significant difference in these two groups ($p<0.05$). All stage IV patients died within 1 year (Figure 2B).

The local control rate was 42.1%. However, one-year survival was 47.4% and 5-year survival was 36.8%.

Discussion

Eeles *et al*. reported on 103 cases of head and neck sarcoma between 1944 and 1988 (4). The average age of their patients was 36 years with no particular difference with respect to gender; the presence of distant metastasis had a great effect on prognosis. Although the average age of their patients was younger than that of our patients, our results were very similar in other respects. Consistent with our findings, Bentz *et al*. reported that prognosis was poor for patients with tumor size >50 mm (5). Pathological diagnosis is far from easy; however, recently, immunostaining and genetic analysis have been used for diagnosis (6, 7). The EWS-FLI-1 translocation between chromosomes 11 and 22 in Ewing's sarcoma is already quite well known and many new chromosomal aberrations are still being reported (7). Although appropriate

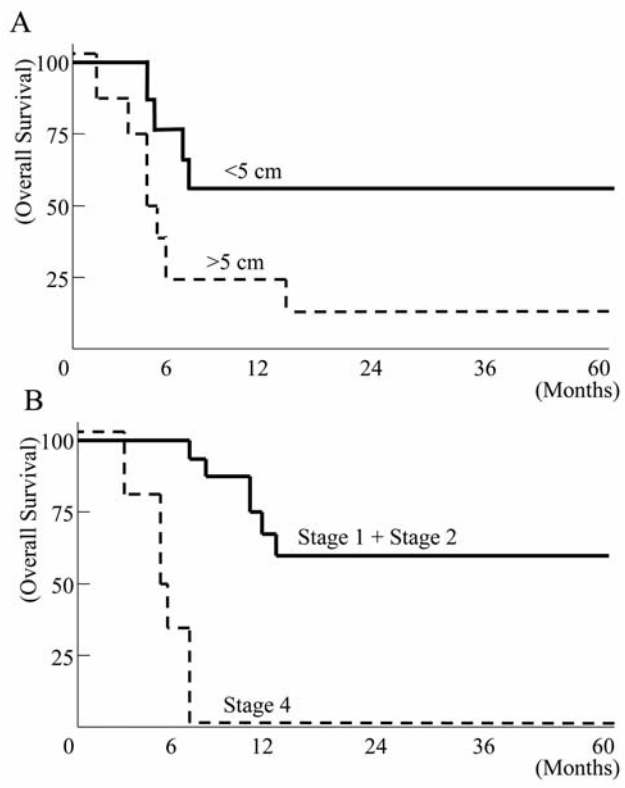

Figure 2. *A: Survival curve of patients with sarcomas in the oral region (n=19) using the Kaplan-Meier method analyzed by the tumor size (<50 mm and >50 mm). B: Survival curve of patients using the Kaplan-Meier method analyzed by the clinical stage according to UICC classification of bone and soft tissue.*

standard treatments have been established for some types of sarcoma, treatment is extremely difficult in particular for rare histological types (6).

In terms of treatment outcomes for osteosarcoma, they have improved drastically in recent years as also for tumors in other parts of the body. Reports suggest that the 5-year survival rate exceeds 60-70% (2). In particular, chemotherapy with methotrexate, adriamycin and cisplatin is regarded extremely effective (8). Compared to osteosarcoma of the arms and legs, the one occurring in the oral cavity has been reported to have better prognosis (9). Some studies have also concluded that tumor diameter and local control are important prognostic factors (6, 10, 11). However, if lung or other metastases are already present on initial examination, complete cure is difficult. We also found similar results in our patients. Moreover, this study reports the results of a 30-year endeavor. Therefore, the survival rate was 33.3%. The regimen of chemotherapy for osteosarcoma was changed in these 30 years. Thus, the majority of the osteosarcomas were old cases that influenced to the low survival rate in this study. Today, there is no answer on how to treat oral osteosarcoma in terms of the relation existing between surgery and chemotherapy. In 3 the institutes, surgery was usually performed firstly in the older osteosarcoma cases. However, the treatment for osteosarcoma has been sifted to chemotherapy.

Freedman *et al*. reported that 4 out of 352 patients (1.1%) with head and neck sarcoma had leiomyosarcoma. In the present study, only 3 cases were identified; regardless, this tumor may be described as rare (12). No method of treatment has been standardized; surgery, chemotherapy and radiotherapy or palliative chemoradiotherapy were performed in our patients.

Malignant fibrous histiocytoma is relatively common in patients with oral sarcomas (13); it has even been reported as the most common type of sarcoma occurring in the oral cavity (4). The 5-year survival for this tumor is 69%, which is regarded as good for sarcomas (4). Consistent with this finding, 2 out of the 3 patients in our study survived, although our sample size was small. It was with the report of Waters *et al*. on this type of tumor that a range of genetic diagnostic methods began to be discovered (14-16).

The prevalence of rhabdomyosarcoma is also believed to be only around 1% of oral sarcomas, thus making this tumor rare (17). In the present study, we found 2 cases, neither of whom could be saved. Age may be a prognostic factor for this tumor, with patients aged <11 years with tumors of <50 mm having a good prognosis (17). Patients with metastasis naturally have a poor prognosis and both cases in our study were aged over 11 years and had metastases.

Angiosarcoma is a rare tumor that most commonly occurs in the head and neck (18). The five-year survival rate is extremely poor at around 10% but, as seen in the present study, the lives of patients with small tumors may be saved if the tumor can be resected with a wide margin. It is helpful if the tumor location permits for surgical resection with a wide margin; however, this may not necessarily be possible in the anatomically restricted head and neck area. Future hopes rest on drugs, such as vascular epithelial growth factor inhibitors, and the development of novel therapies (18).

A number of other tumors of extremely unusual histological types were also identified, such as malignant schwannoma and malignant rhabdoid tumor; however, treatment methods for any of these tumors are yet to be established as none of the patients in this study could be saved. Sarcomas proliferate invasively with frequent metastasis (19, 20) and the key to saving patients may lie in how quickly the lesions can be identified and surgically resected. Particularly, for unusual tumors like these, chemotherapy and radiotherapy should be regarded as ineffective when deciding treatment strategy. There is no uniform treatment protocol for oral sarcoma. However, there is an interesting study using both surgery and radiotherapy

Table I. *Summary of 19 patients with sarcoma.*

	Age, gender	Site	Size (mm)	Histology	T	Rec.	M	P
1	17, ♀	Mandible	56×54	Osteosarcoma	S+C	N/A	Lung	Dead
2	44, ♂	Maxilla	23×13	Osteosarcoma	S	None	None	Alive
3	61, ♀	Mandible	55×50	Osteosarcoma	S+C	N/A	Lung, bone	Dead
4	62, ♀	Mandible	30×30	Osteosarcoma	S	11M	None	Alive
5	64, ♂	Maxilla	60×50	Osteosarcoma	S+C	None	Bone	Dead
6	80, ♀	Mandible	70×70	Osteosarcoma	S+R+C	10M	None	Dead
7	29, ♂	Mandible	32×22	Leiomyosarcoma	S+R+C	1Y6M	Lung	Alive
8	56, ♂	Mandible	40×20	Leiomyosarcoma	S+R+C	8M	None	Dead
9	76, ♂	Maxilla	57×40	Leiomyosarcoma	R+C	N/A	Lung	Dead
10	31, ♂	Cheek	24×24	MFH	S+C	None	None	Alive
11	41, ♂	Cheek	50×50	MFH	S	None	None	Alive
12	55, ♂	Maxi. sinus	55×40	MFH	S+R+C	10M	Bone	Dead
13	21, ♀	Maxilla	25×10	Rhabdomyosarcoma	S+R+C	3M	Bone	Dead
14	40, ♀	Mandible	42×25	Rhabdomyosarcoma	S+R+C	None	Bone	Dead
15	55, ♀	Mandible	19×10	Angiosarcoma	S	None	None	Alive
16	64, ♀	Mandible	50×40	Ewing's sarcoma	S+R+C	5M	Lung	Dead
17	45, ♂	Mandible	26×25	Malignant schwanoma	S+R+C	5M	Bone	Dead
18	64, ♀	Neck	25×16	Rhabdoid tumor	R+C	N/A	Lung	Dead
19	68, ♂	Maxilla	35×25	Undifferentiated sarcoma	S	None	None	Alive

S, Surgery; R, radiotherapy; C, chemotherapy; MFH, malignant fibrous histiocytoma; T, treatment; Rec., recurrence; N/A, not available; M, metastasis; P, prognosis.

Table II. *Summary of the patients by tumor stage.*

Stage	Total number	Recurrence	Metastasis	Alive	Dead
I	8 patients	5 (63%)	4 (50%)	4 (50%)	4 (50%)
II	5 patients	2 (40%)	1 (20%)	3 (60%)	2 (40%)
III	0	0	0	0	0
IV	6 patients	4 (66%)	6 (100%)	0	6 (100%)

According to UICC classification of bone and soft tissue.

to improve locoregional control that may contribute to the "quality of life" of oral sarcoma patients (21). Most of the reports are case studies. The cases of HIV-related Kaposi's sarcoma were also sometimes reported (22, 23).

In terms of the neck node status, only one case (case number 9) had neck node metastases. This is a rare case because oral sarcomas rarely metastasize to the neck lymph nodes. There was no case to perform neck dissection.

As mentioned above, the size of the primary tumor and the presence of distant metastasis are the most important prognostic factors (4, 5), which was also found in our present study. Patients with sarcomas having a diameter over 50 mm had an extremely poor prognosis and a higher rate of distant metastasis. If distant metastasis is present, it affects the prognosis; however, metastasis was absent in almost all surviving patients. In terms of chemotherapy, chemo-radiotherapy with cyclophosphamide, vincristine, adriamycin and dacarbazine was performed in all cases except osteosarcoma. Unfortunately, this therapy was not effective. As in the case of other malignant tumors, early discovery and treatment are important when dealing with oral sarcoma; for tumors with histological types that are unresponsive to chemotherapy and radiotherapy, wide-range surgical resection is desirable.

In the present study, we found that tumor diameter and distant metastasis were important prognostic factors for patients with oral sarcoma. The tumors occurring in the oral region can be observed clearly and should be identified and surgically resected at the earliest possible stage. This early resection may help prevent distant metastasis (24).

Conflicts of Interest

None of the authors has a financial conflict of interest to disclose in relation to the content of this article.

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