Observational Study

Medicine®

OPEN

Prognosis of osteosarcomas in the mandible: 15-year experience of 55 patients

Dongjie Seng, MD[a], Junfu Wu, MD[b,*], Qigen Fang[b,*], Fei Liu, MD[c]

Abstract

Our goal was to evaluate the prognosis of osteosarcomas (OS) in the mandible for finding out the best treatment.

Patients diagnosed with OS in the mandible from January 2000 to December 2015 were retrospectively enrolled. Demographic, tumor-specific, treatment, and survival data were collected and analyzed.

A total of 55 patients (35 male and 20 female) were included, all patients had first manifestation of swelling. Cachexia occurred in 15 (27.3%) patients. Chondroblastic type was the most common histology subtype followed by osteoblastic type. High grade tumors were found in 30 (63.6%) patients. 33 (60%) patients received an operation of hemimandibulectomy, and free fibula reconstruction was performed in 20 (36.4%) patients. The 5-year recurrence-free survival (RFS) and disease-specific survival (DSS) rates were 73.6% and 66.9%, respectively. Univariate prognostic analysis reported risk factors of tumor grade, reconstruction type (free fibula flap vs non-free flap), and operation extent were significant for the recurrence, and reconstruction type and operation extent were significant for the disease-specific death, but in multivariate analysis, only the factor of operation extent was significantly associated with both the recurrence and death.

A wide excision extent such as hemimandibulectomy is suggested for OS in the mandible for achieving good prognosis.

Abbreviations: DSS = disease specific survival, OS = Osteosarcomas, RFS = recurrence free survival.

Keywords: head neck, hemimandibulectomy, mandible malignancy, osteosarcomas

1. Introduction

Osteosarcomas (OS) is the most common primary malignant tumor of bone, nearly 6% of which occurs in the jaw mainly the mandible.[1] Difference regarding clinical presentation and biologic behavior have been well established.[2–5] In OS of long bone, the average age of onset is 10 to 20 years earlier, the histopathologic variables are less favorable, distant metastasis occurs more frequently, and the survival rate is poorer. Owing to advent of (neo-) adjuvant chemotherapy, the 5-year overall survival rate of long bone OS has increased to 60% to 70%,[1] but similar trend in jaw OS could not be seen. The most common histopathologic type is chondroblastic type in head and neck group and osteoblastic in extremity group.[1] Moreover, tumor-positive margin exists more frequently in head and neck OS, and local recurrence was the most common treatment failure on account of probable technical difficulty to achieve clear margins because of delicate and complicated anatomy.[6,7]

Because of the rarity, knowledge of jaw OS is limited to small single studies with uncertainty in the optimal treatment. Few authors have tried to evaluate how the excision extent affects the survival. Role of chemotherapy and radiotherapy also remains unclear. In a study published by Mardinger et al,[2] there were 6 cases in the mandible, and the authors concluded that the introduction of chemotherapy did not dramatically alter the prognosis of OS of the jaw, similar results were also reported by Granowski-LeCornu et al.[3] However, a recent meta-analysis described significant advantage for disease-free and overall survival by the use of chemotherapy.[8]

Therefore, the present study aimed to investigate the prognosis of the mandible OS for finding out the best treatment with a focus on whether a wide excision could improve the survival.

2. Methods

The Zhengzhou University institutional research committee approved our study and all participants signed an informed consent agreement, and all experiments were performed in accordance with relevant guidelines and regulations.

Patients diagnosed with the mandible OS from January 2000 to December 2015 were identified by reviewing medical records. Patients with recurrent disease were excluded. Primary data extracted from the database included the following: age, sex, cachexia, histologic subtype, resection extent, reconstruction type, tumor grade, tumor stage, margin status, radiotherapy, and follow-up information and so on. Cachexia was diagnosed as a BMI of less than 20 kg/m^2 and ongoing weight loss of more than 2%; or weight loss of >5% over past 6 months; or sarcopenia and

Editor: Li Wu Zheng.

The authors have no conflicts of interest to disclose.

[a] Department of Otohinolaryngology, Children's Hospital to Zhengzhou University, Zhengzhou University, Zhengzhou, [b] Department of Head and Neck, Affiliated Cancer Hospital of Zhengzhou University, [c] Department of Oral Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

[*] Correspondence: Junfu Wu, Department of Head and Neck, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China (e-mail: hnzlyyjxq@163.com); Qigen Fang, Zhengzhou university, Zhengzhou, henan CHINA (e-mail: qigenfang@126.com).

Medicine (2019) 98:1(e13875)

Received: 26 August 2018 / Received in final form: 23 October 2018 / Accepted: 4 December 2018

http://dx.doi.org/10.1097/MD.0000000000013875

ongoing weight loss of more than 2%. For the purpose of the research, grade I and II were defined to be low-grade tumor, and grade III and IV were defined to be high-grade tumor. All the disease was re-staged based on the 8th edition of AJCC TNM classification.

Univariate and multivariate analysis (Cox-proportional hazard model) were used to determine the prognostic factor for the recurrence and disease-related death; lost patients were also included in survival analysis as censored value. And Kaplan Meier analysis was used to calculate the recurrence-free survival (RFS) and disease-specific survival (DSS) rates. All statistical analyses were performed using SPSS 13.0. A $P<.05$ was considered significant.

3. Results

A total of 55 patients (35 male and 20 female) were enrolled with a mean age of 32.5 (range: 14–66) years. All patients had first manifestation of swelling, of whom 10 (18.2%) patients complaint local pain, 6 (10.9%) patients had lower lip numbness and 3 (5.5%) patients complaint difficulty in opening mouth. There were no loose teeth. Cachexia occurred in 15 (27.3%) patients. No previous history of head and neck radiation, trauma, Li-Fraumeni syndrome was reported.

Histology subtype of osteoblastic was seen in 15 (27.3%) patients, chondroblastic in 20 (36.4%) cases, fibroblastic in 11 (20%) patients, and mix in 9 (16.4%) patients. High-grade tumors were found in 30 (63.6%) patients, and low grade in 25 (36.4%) patients. At presentation, stage of 1A was recorded in 11 (21.2%) patients, 1B in 12 (23.1%) cases, 2A in 21 (40.3%) cases, and 2B in 8 (15.4%) cases. Stage of 3 (5.5%) patients was unknown.

All patients underwent primary tumor resection, of which 33 (60%) patients received an operation of hemimandibulectomy, 22 (40%) patients underwent partial mandibulectomy. Free fibula reconstruction was performed in 20 (36.4%) patients, and iliac bone graft in 15 (27.3%) patients. Positive margin (all soft tissue) was reported in 5 (9.1%) patients. All the patients received adjuvant chemotherapy (methotrexate, cisplatin, doxorubicin, and cyclophosphamide), and 5 patients also underwent postoperative radiotherapy.

Mean follow-up time was 63.3 (range: 20–163) months, 8 (14.6%) patients were lost. Recurrence occurred in 16 (29.1%) patients: locally in 8 (50%) cases, distantly in 5 (31.2%) cases, locally as well as distantly in 3 (18.8%) cases. 12 patients died of the disease. As described in Table 1, compared to non-survivors, cancer survivors had significantly wider resection extent ($P=.016$), there was no apparent difference regarding other variables between survivors and non-survivors (all $P>.05$).

The overall 5-year RFS and DSS rates were 73.6% and 66.9%, respectively (Fig. 1 and Fig. 2). The 5-year RFS rates in patients with partial mandibulectomy or hemimandibulectomy were 41% and 71%, respectively, the difference was significant ($P=.013$, Fig. 3). The 5-year DSS rates in patients with partial mandibulectomy or hemimandibulectomy were 23% and 89%, respectively, the difference was significant ($P=.006$, Fig. 4).

Prognostic analysis reported risk factors of tumor grade, reconstruction type (free fibula flap vs non-free flap), and operation extent were significant for the recurrence in univariate analysis (Table 2), and reconstruction type (free fibula flap vs non-free flap) and operation extent were significant for the disease-related death in univariate analysis (Table 3), but in multivariate analysis, only the factor of operation extent was significantly associated with both the recurrence ($P=.004$, HR (95% CI): 0.095 (0.017–0.547)) and disease-related death ($P=.008$, HR (95% CI): 0.095 (0.017–0.547)). (Tables 2 and 3).

Table 1

Comparison of demographic data between survivors and non-survivors*.

	Survivor (n = 35)	Non-survivor (n = 12)	P
Age			
≤32	19	3	
>32	16	9	.079
Sex			
Male	24	6	
Female	11	6	.306
Cachexia			
Yes	10	3	
No	25	9	1.000
Histology subtype			
Osteoblastic	11	3	
Chondroblastic	11	3	
Fibroblastic	7	4	
Mix	6	2	.857
Tumor grade			
High	16	7	
Low	19	5	.450
Tumor stage			
1A+1B	17	6	
2A+2B	18	6	1.000
Resection extent			
Hemi	26	4	
Partial	9	8	.016
Reconstruction type			
Free fibula flap	12	8	
Non-fibula flap	23	4	.089
Margin status			
Positive	3	2	
Negative	32	10	.590
Radiotherapy			
Yes	4	1	
No	31	11	1.000

* 8 patients were lost and excluded in this analysis.

4. Discussion

Demographic characteristics reported in the present study was comparable to other researches.[2–7] Mandible OS usually developed in the third and fourth decades of life, and male patients were more frequently affected. Swelling without pain was the most common complaint, sensation dysfunction was less common, and it was noted that difficulty of mouth-opening occurred in 5.5% of the patients, few authors had reported the situation. The most common histologic subtype was osteoblastic and chondroblastic.

Cancer cachexia was a multifactorial metabolic syndrome associated with an underlying malignant disease. It was characterized by weight loss, decreased appetite, inflammatory state, and metabolic alterations. Clinical features in patients with cachexia were skeletal muscle mass and function, loss of adipose tissue, resulting in progressive loss of body weight. As high as 42% of patients diagnosed with head-neck squamous cell carcinoma were reported to suffer from cachexia,[9] and even Orell-Kotikanqas et al[10] reported the DSS was 13 months (3–62) in cachectic patients, compared with 66 months (31–78) in non-cachectic patients ($P=.009$). However, detailed description

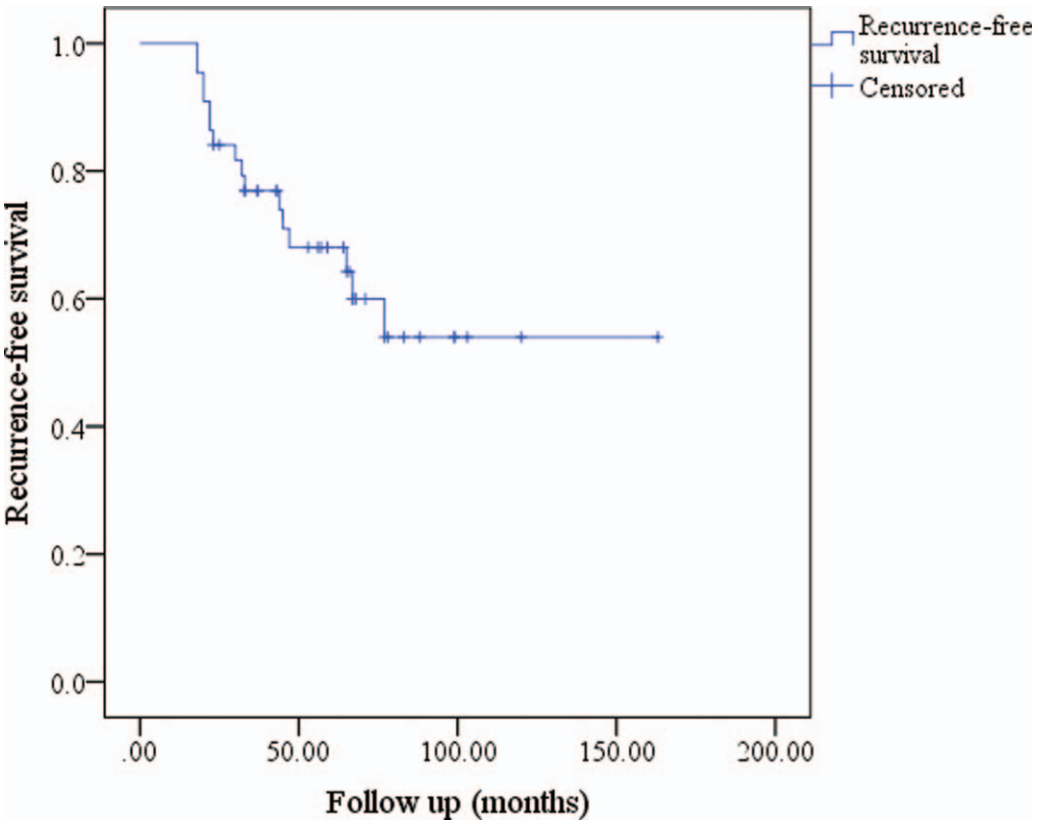

Figure 1. Recurrence free survival rate of the patients.

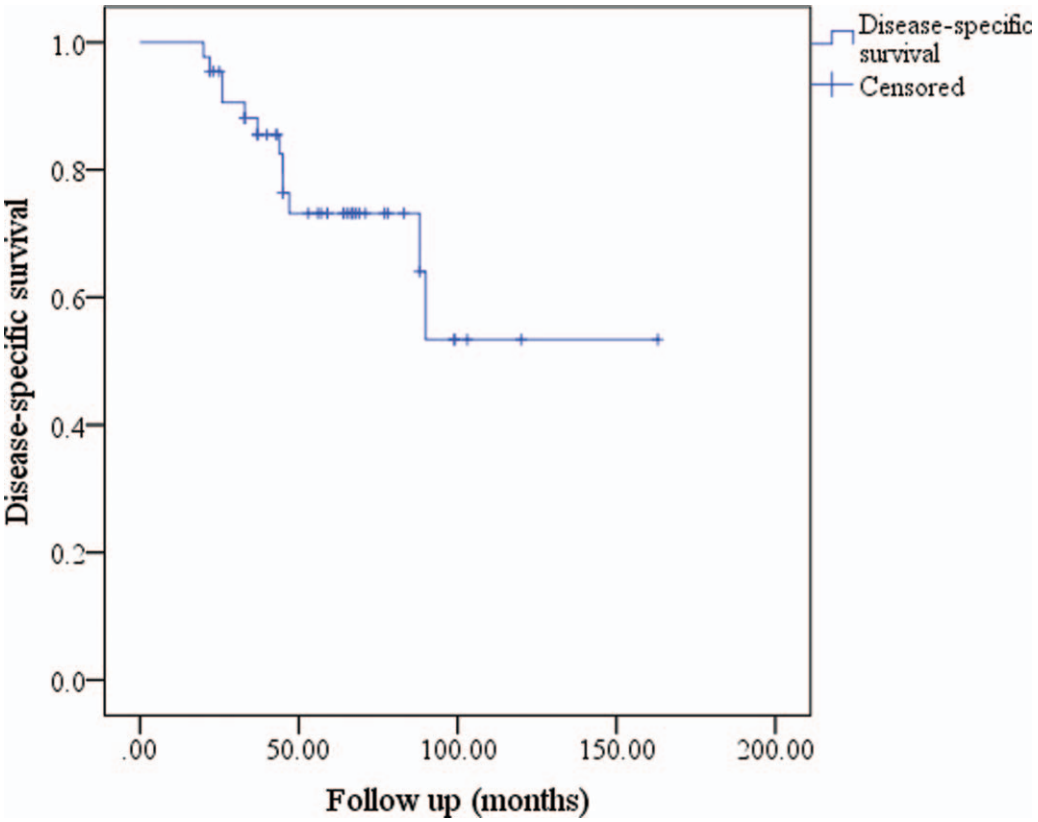

Figure 2. Disease specific survival rate of the patients.

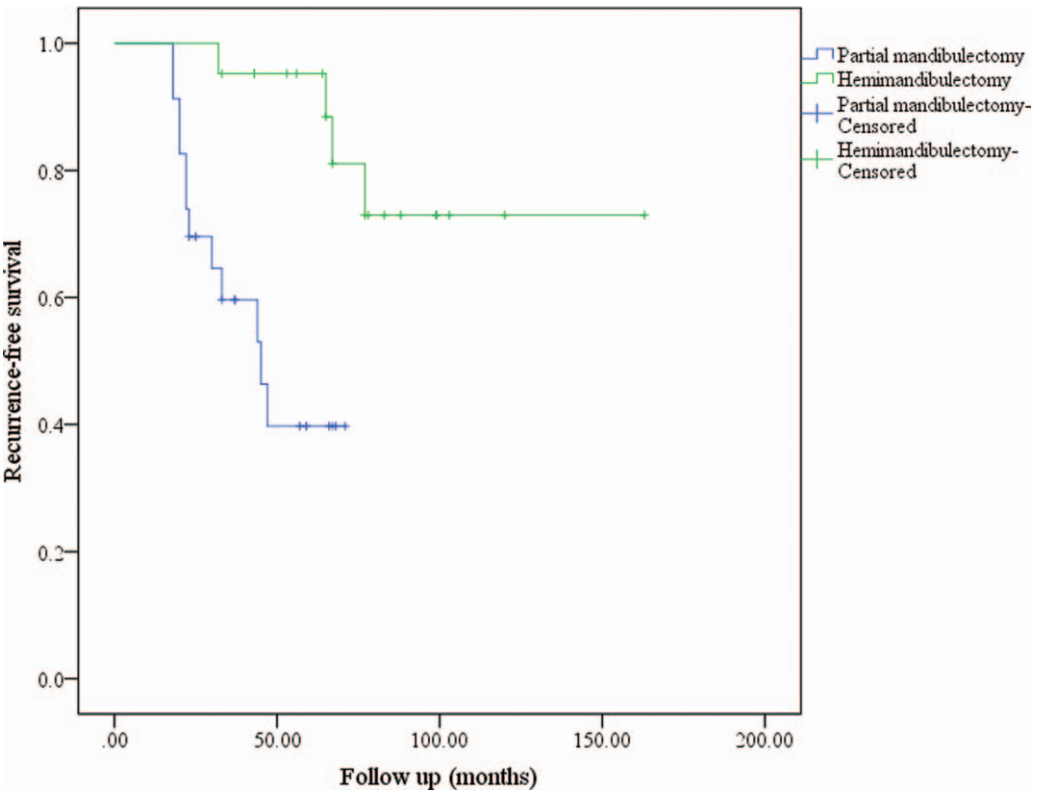

Figure 3. Recurrence-free survival in patients with different resection extent ($P = .013$).

of cachexia in the mandible OS remained unclear. In previous literature, only Granowski-LeCornu et al[3] easily reported 8% of their patients had weight loss, and it was significantly associated with decreased survival. However, clinical manifestation of cachexia included innutrition, muscle dysfunction, insomnia and so on, not just weight loss. We were the first to depict the rate of cachexia was 27.3% in mandible OS, a little lower than that in squamous cell carcinoma of head neck. The possible reason was that in patients with head-neck squamous cell carcinoma, more factors were involved in contributing to the occurrence of cachexia, there were more complaint of pain, poor oral hygiene, dysphagia, and cachexia was often accompanied by anorexia, which was caused by production of pro-inflammatory cytokines, it was associated with the predominance of anorexigenic signals and lack of orexigenic signals. However, we were failure to find out a positive correlation between cachexia and survival, there was bias might be caused by the relatively small sample size.

A little better prognosis was noted in present study compared to the first paper consisting of a Chinese population published by Chen et al,[7] possible explanation was that: first, the present study only included OS of the mandible, and previous authors had described that the 5-year survival rate of patients with mandible OS was about 10% higher than that the patients with tumors located in the maxilla and the skull base.[7] Second, there was lower positive margin rate, and the study had proved that positive margin was significantly associated with the RFS, similar finding was also reported by Patel et al.[11] Third, most of our patients received an operation of hemimandibulectomy, and in a report by Mardinger et al,[2] the patients undergoing hemimandibulectomy were all alive at the last follow-up.

Significance of complete resection was the key for treating the mandible OS, clear margin could be achieved more easily in the mandible than in the maxilla or skull base,[2,3] less than 10% of the patients had positive margin. The exact operation extent of resecting the tumor remained unclear, some authors had recommended hemimandibulectomy as a standard procedure for any OS arising proximal to the parasymphyseal region.[12,13] And in a recent study published by Mardinger et al,[2] the patients undergoing hemimandibulectomy were all alive at the last follow-up. The finding might suggest that a wider margin might improve the survival. In present study, it was noted that compared to partial mandibulectomy, hemimandibulectomy was associated with better RFS and DSS rates in multivariate analysis. Possible reasons for the finding were based on the following consideration: first, we wanted to have a wider surgical margin which might mean better prognosis; second, ability of free fibula flap reconstruction in our cancer center provided us with more confidence without worrying decreasing the patients' quality of life, and many researches had described poorer postoperative quality of life was related with poorer prognosis;[14] third, local recurrence was the most common treatment failure, and it hoped that more extensive surgical resection could decrease the failure rate.

Role of chemotherapy in treating mandible OS remained controversy. Patel et al[11] presented limited survival benefit was noticed by applying of chemotherapy in Memorial Sloan-Kettering Cancer Center, but Smeele et al[8] reviewed pooled data from 201 patients of head neck OS published from 1974 to 1994, the meta-analysis stratified for use or non-use of chemotherapy as well as completeness of resection, and the authors concluded chemotherapy improved survival in craniofacial OS and advocated the adoption of the chemotherapy protocols used for OS of the long bones for craniofacial OS, the finding was also supported by a recent study from China.[15] All

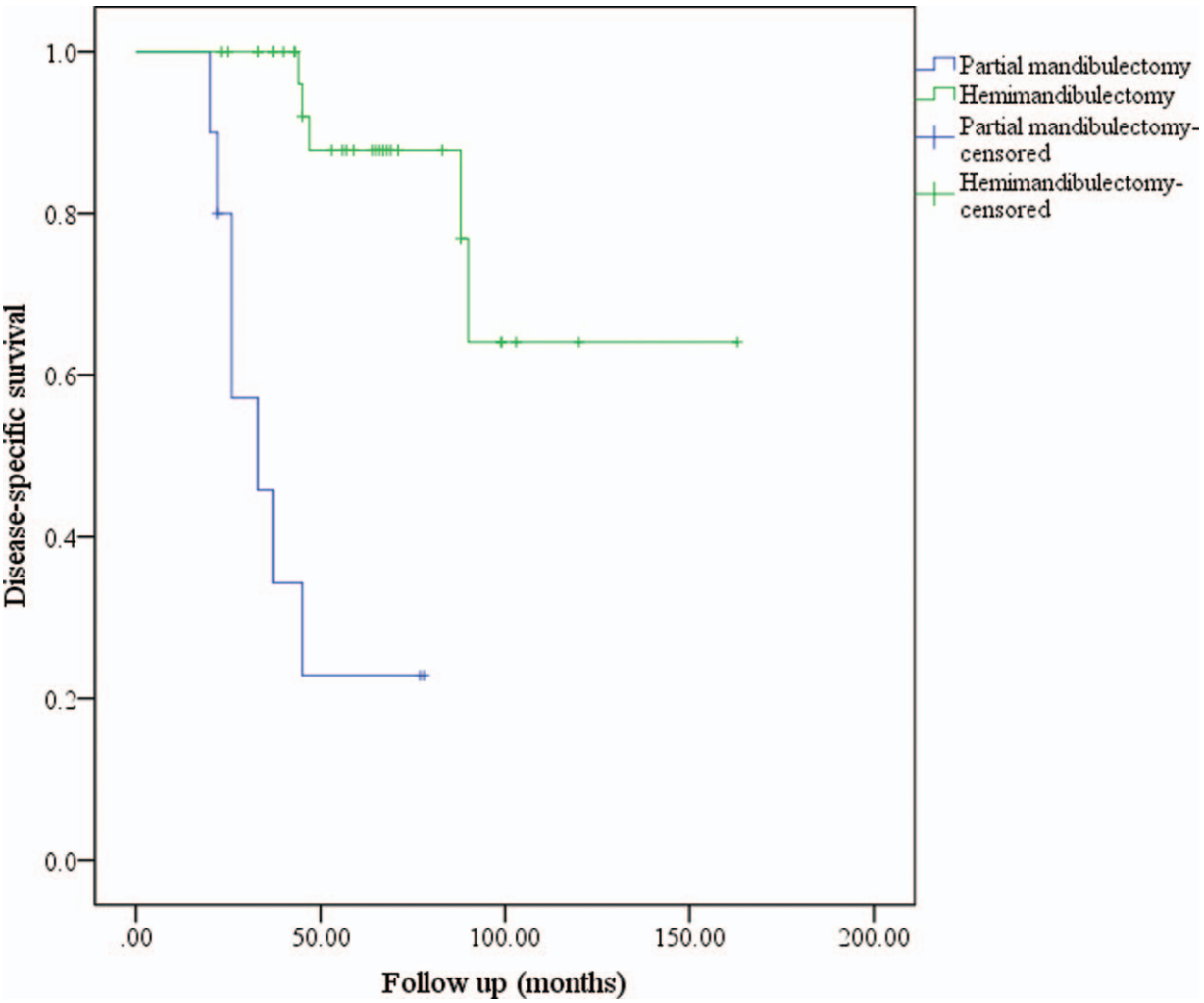

Figure 4. Disease-specific survival in patients with different resection extent ($P = .006$).

patients received chemotherapy in present study, it might lead to the relatively satisfactory survival rate.

OS was relatively radioresistant, and radiotherapy was used in cases where clear margin could not achieve, as we had performed. A recent paper published by Chen et al[15] pointed that adjuvant radiotherapy improved local control of head and neck OS. Inspiringly, de Miguel GC et al[16] had aimed to develop murine models of vertebral and cranial osteosarcoma that facilitate simple clinical monitoring and real-time imaging to evaluate the outcome of photodynamic therapy, and the authors described that after photodynamic therapy, scintigraphy showed lower tumoral radiopharmaceutical uptake, which was associated

Table 2

Univariate and cox model analysis of risk factors for recurrence.

	Univariate (log-rank)	Cox model	
Variable	*P*	*P*	HR (95% CI)
Age	.954		
Sex	.599		
Cachexia	.851		
Histologic subtype	.518		
Reconstruction type	.013	.331	3.136 (0.298–17.330)
Tumor stage	.820		
Tumor grade	.023	.110	5.170 (0.774–23.187)
Margin status	.061		
Radiotherapy	.259		
Resection extent	.005	.004	0.013 (0.001–0.246)

Table 3

Univariate and cox model analysis of risk factors for death.

	Univariate (log-rank)	Cox model	
Variable	*P*	*P*	HR (95% CI)
Age	.145		
Sex	.347		
Cachexia	.686		
Histologic subtype	.655		
Reconstruction type	.014	.063	4.883 (0.917–25.990)
Tumor stage	.853		
Tumor grade	.298		
Margin status	.051		
Radiotherapy	.104		
Resection extent	.002	.008	0.095 (0.017–0.547)

histologically with increased necrosis. Moreover, tumor size decreased, and osteoid matrix volume increased in all photodynamic therapy-treated animals. Therefore, photodynamic therapy was a potential antitumoral treatment for surgically inoperable osteosarcoma in the future.[16]

In summary, operation extent was the most important prognostic factor, and a wide excision extent such as hemimandibulectomy is suggested for OS in the mandible for achieving good prognosis.

Author contributions

Conceptualization: Dongjie Seng, Junfu Wu.
Data curation: Dongjie Seng.
Formal analysis: Dongjie Seng.
Funding acquisition: Dongjie Seng.
Investigation: Dongjie Seng.
Methodology: Dongjie Seng, Junfu Wu, Fei Liu.
Project administration: Dongjie Seng, Junfu Wu.
Resources: Dongjie Seng, Junfu Wu.
Software: Dongjie Seng, Junfu Wu, Fei Liu.
Supervision: Dongjie Seng, Qigen Fang.
Validation: Dongjie Seng.
Visualization: Dongjie Seng.
Writing – original draft: Dongjie Seng.
Writing – review & editing: Dongjie Seng.

References

[1] Durnali A, Alkis N, Cangur S, et al. Prognostic factors for teenage and adult patients with high-grade osteosarcoma: an analysis of 240 patients. Med Oncol 2013;30:624.
[2] Mardinger O, Givol N, Talmi YP, et al. Osteosarcoma of the jaw: the Chaim Sheba Medical Center experience. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:445–51.
[3] Granowski-LeCornu M, Chuang SK, Kaban LB, et al. Osteosarcoma of the jaws: factors influencing prognosis. J Oral Maxillofac Surg 2011;69:2368–75.
[4] Fernandes R, Nikitakis NG, Pazoki A, et al. Osteogenic sarcoma of the jaw: a 10-year experience. J Oral Maxillofac Surg 2007;65:1286–91.
[5] Lee RJ, Arshi A, Schwartz HC, et al. Characteristics and prognostic factors of osteosarcoma of the jaws: a retrospective cohort study. JAMA Otolaryngol Head Neck Surg 2015;141:470–7.
[6] Oda D, Bavisotto LM, Schmidt RA, et al. Head and neck osteosarcoma at the University of Washington. Head Neck 1997;19:513–23.
[7] Chen Y, Shen Q, Gokavarapu S, et al. Osteosarcoma of head and neck: a retrospective study on prognostic factors from a single institute database. Oral Oncol 2016;58:1–7.
[8] Smeele LE, Kostense PJ, van der Waal I, et al. Effect of chemotherapy on survival of craniofacial osteosarcoma: a systematic review of 201 patients. J Clin Oncol 1997;15:363–7.
[9] Jager-Wittenaar H, Dijkstra PU, Dijkstra G, et al. High prevalence of cachexia in newly diagnosed head and neck cancer patients: an exploratory study. Nutrition 2017;35:114–8.
[10] Orell-Kotikangas H, Österlund P, Mäkitie O, et al. Cachexia at diagnosis is associated with poor survival in head and neck cancer patients. Acta Otolaryngol 2017;137:778–85.
[11] Patel SG, Meyers P, Huvos AG, et al. Improved outcomes in patients with osteogenic sarcoma of the head and neck. Cancer 2002;95:1495–503.
[12] Pease GL, Maisel RH, Cantrell RW. Surgical management of osteogenic sarcoma of the mandible. Arch Otolaryngol 1975;101:761–2.
[13] Russ JE, Jesse RH. Management of osteosarcomas of the maxilla and mandible. Am J Surg 1980;140:572–6.
[14] Ringash J. Survivorship and quality of life in head and neck cancer. J Clin Oncol 2015;33:3322–7.
[15] Chen Y, Gokavarapu S, Shen Q, et al. Chemotherapy in head and neck osteosarcomas: adjuvant chemotherapy improves overall survival. Oral Oncol 2017;73:124–31.
[16] de Miguel GC, Abrantes AM, Laranjo M, et al. A new therapeutic proposal for inoperable osteosarcoma: Photodynamic therapy. Photodiagnosis Photodyn Ther 2018;21:79–85.