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High-Grade Surface Osteosarcoma: Clinical Features and Oncologic Outcome

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ABSTRACT

Background: High-grade surface osteosarcoma is an extremely rare subtype of osteosarcoma. The treatment outcome for this tumor varies in different centers.
Methods: This was a retrospective study of high-grade surface osteosarcoma; clinical, radiological, and histological materials were reviewed.
Results: We studied 23 patients (16 males, seven females); median age was 24 years old. All the tumors involved the lower limb, located at the diaphysis in 11 patients and at the metaphysis in 12 patients. Even though the majority of tumors were located at the surface of the bone, the medullary canal was involved in 10 patients. The microscopic findings were indistinguishable from conventional central osteosarcoma. All the patients were treated with a combination of surgery and systemic chemotherapy. Follow-up data were completed in 20 patients; follow-up duration ranged from 27 months to 182 months or until the patient died of the disease (5–104 months). Of the 20 patients, 12 died of the disease, and eight patients were alive at the time of the last follow-up. The 5-year overall survival rate was 37.6%.
Conclusions: Our study revealed that the treatment outcome for this tumor shows a poor survival rate.

Introduction

Surface osteosarcomas are a group of rare tumors arising from the surface of bone. There are three subtypes of surface osteosarcomas: parosteal osteosarcoma, periosteal osteosarcoma, and high-grade surface osteosarcoma. Parosteal osteosarcoma, a low-grade tumor, is the most common subtype where wide resection generally confers a good outcome. Periosteal osteosarcoma, an intermediate-grade tumor, is similarly well controlled by wide resection [1]. High-grade surface osteosarcoma is the rarest of the three subtypes. First reported in 1964 by Francis et al [2], high-grade surface osteosarcoma was found in the two patients reported to have a similar prognosis as conventional central osteosarcoma. Other studies published subsequently have expanded on our understanding of this rare disease [3-11]. Treatment for this disease is similar to high-grade osteosarcoma, and involves wide resection and chemotherapy. Published series are mostly from European and North American institutions, with many including patients prior to the advent of modern chemotherapy. Contemporary series from other centers can provide us with a means of better understanding this rare condition with respect to its clinical features and the oncologic outcomes.

Materials and methods

The prospectively collected musculoskeletal oncology database of our hospital was queried to identify patients diagnosed with high-grade surface osteosarcoma from 1992 through 2015. Patients were included if they had osteosarcoma arising on the surface of bone and where high-grade osteosarcoma was present histologically. While patients were excluded if they were diagnosed with dedifferentiated parosteal osteosarcoma, where a focus of high-grade sarcoma was juxtaposed against a background of a parosteal osteosarcoma. Patients with periosteal osteosarcoma were also excluded by pathologist.

From 1992 through 2015, 23 patients were treated in our hospital who matched the inclusion criteria. The study group included 16 males

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and seven females, with a median age of 24 years (Range: 14 - 57 years)

The diagnosis of high-grade surface osteosarcoma was confirmed on biopsy in all patients following clinical and radiologic workup. The treatment regimen for individual patients was made through multidisciplinary team discussion. All the patients were treated with a combination of surgery and systemic chemotherapy. The chemotherapy regimen involved the use of high-dose methotrexate, ifosfamide, doxorubicin, and cisplatin.

All the patients underwent surgery in our hospital as a component of the initial treatment. Where the extent of the disease made an adequate surgical margin difficult to achieve for limb salvage surgery, neoadjuvant chemotherapy was administered. Where the surgical margin for limb salvage surgery was not difficult or in some cases amputation was considered, the neoadjuvant chemotherapy wasn't administered and only post-operative chemotherapy was given. All the patients received post-operative chemotherapy.

Data were collected on demographic characteristics of subjects, tumor related features, the nature of surgical and medical treatment, and the occurrence of any significant events related to the malignancy (ie. Local recurrence, metastasis, death). Patient data regarding certain tumor-related and treatment-related factors was collected for analysis. The factors assessed included age, gender, anatomic location, medullary extension of the lesion, surgical margin and neoadjuvant chemotherapy was administered.

Three patients treated before 2000 were excluded from the survival analysis. In two patients, the follow-up durations were only 3 months and 7 months before they defaulted follow up. In another patient the follow-up time was long but still excluded owing to the changes in chemotherapy regimens prior to and after 2000 to better reflect the outcomes of contemporary management.

The data were reviewed and tabulated for statistical analysis. Descriptive statistics were calculated and Kaplan-Meier survival analysis was performed to assess survival outcomes. The log rank test was used for comparing survival outcomes in subgroups. IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY, USA) was used for survival analysis.

Results

Clinical presentation and radiological findings

The distribution of age, gender, and anatomic location are shown in Fig. 1. All the patients presented with pain and swelling of the affected limb; the median duration of symptoms was 6 months (range 3–8 months). All the cases of this occurred in the lower limb: proximal femur (n = 1), femoral diaphysis (n = 6), distal femur (n = 8), proximal tibia (n = 3), tibial diaphysis (n = 4) and distal fibula (n = 1).

All the patients were evaluated with CT scans preoperatively, and all but one underwent a preoperative MRI scan. Cross-sectional imaging confirmed the surface based nature of all the lesions. The lesion was located at the diaphysis in 11 patients, and in the metaphysis in 12 patients. Medullary invasion was noted radiologically in 10 patients, however in those patients the majority of the tumor was still were located at the surface of the bone. The radiologic studies showed aggressive features in all cases such as bone destruction, periosteal reaction, and a soft tissue component (Fig. 2).

Pathological features

All the specimens were sectioned longitudinally and axially using an electric saw. Medullary canal involvement was evaluated macroscopically. Microscopically, the tumors were indistinguishable from conventional central osteosarcoma (Fig. 3). All the tumors were classified as grade 4 osteosarcoma using Broder's grading system. The histologic findings included anaplastic cellular features as well as osteoid and immature bone and cartilage formation, severe cytologic atypia, mitotic activity, and areas of necrosis. None of these tumors had classic features of parosteal osteosarcoma, such as well-differentiated bony trabeculae within fibrous stroma. None of the classic features of periosteal osteosarcoma were found neither. On both macroscopic and microscopic examination, the medullary canal was involved in 10 of 23 patients (43.5%).

Treatment and outcome

The follow-up information regarding treatment and outcome is shown in Table 1. Of the 20 patients included for survival analysis, 12 died of disease while on follow up, and eight patients were alive at the

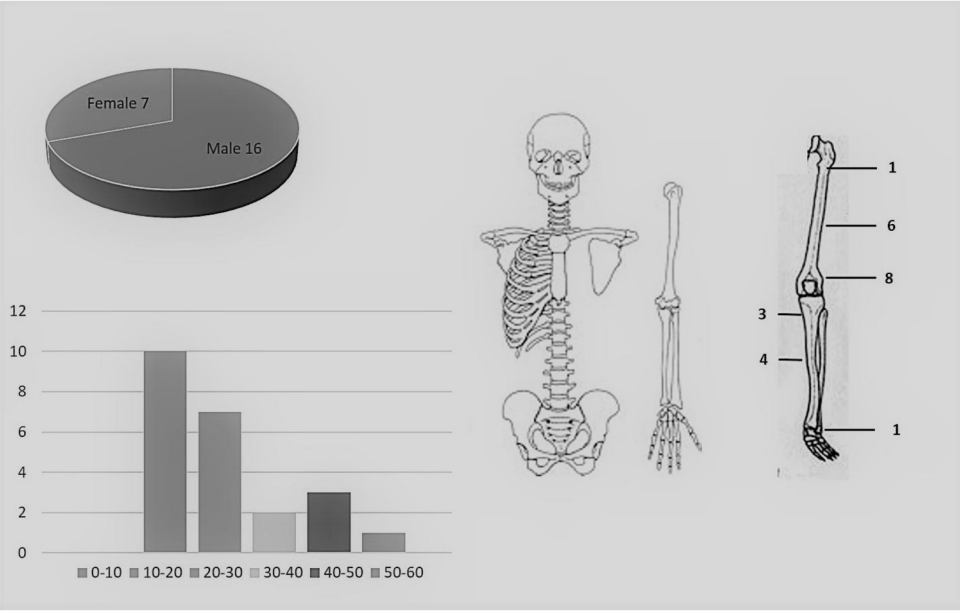

Fig. 1. Distribution by sex, age, and anatomic location of high-grade surface osteosarcoma in 23 patients at our institution.

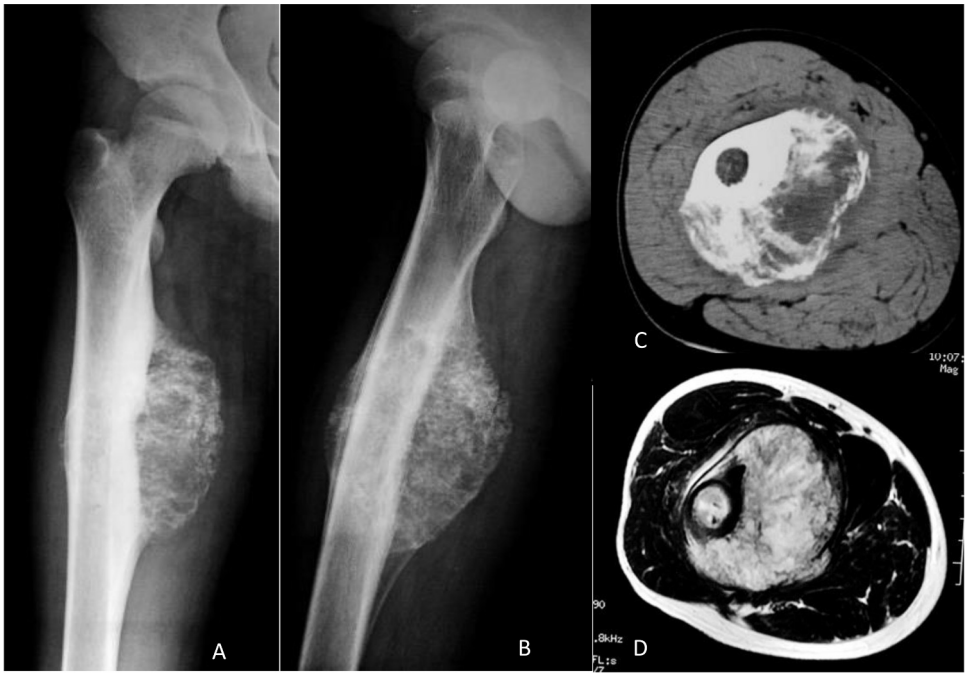

Fig. 2. a and b, anterior-posterior view and lateral view of high-grade surface osteosarcoma at the femur shaft; c, CT scan showed that the soft tissue component and the marrow were not involved in this patient; d, MRI scan showed the extent of soft tissue in this tumor.

time of last follow-up. The follow-up duration ranged from 27 months to 182 months for those alive at last follow up, while survival for those who died of disease ranged from 5 to 104 months from the time of diagnosis.

Regarding adjuvant chemotherapy, six patient received neoadjuvant and adjuvant chemotherapy, while 14 patients underwent postoperative chemotherapy only. Four patients underwent amputation, whereas the remaining 16 patients (80%) underwent limb-sparing surgery. Two patients presented with lung metastasis (Stage III), and the others had only local disease at the time of presentation (Stage IIB). Wide surgical margins were achieved in 15 patients, and marginal margins were achieved in five patients. Local recurrence occurred at 13

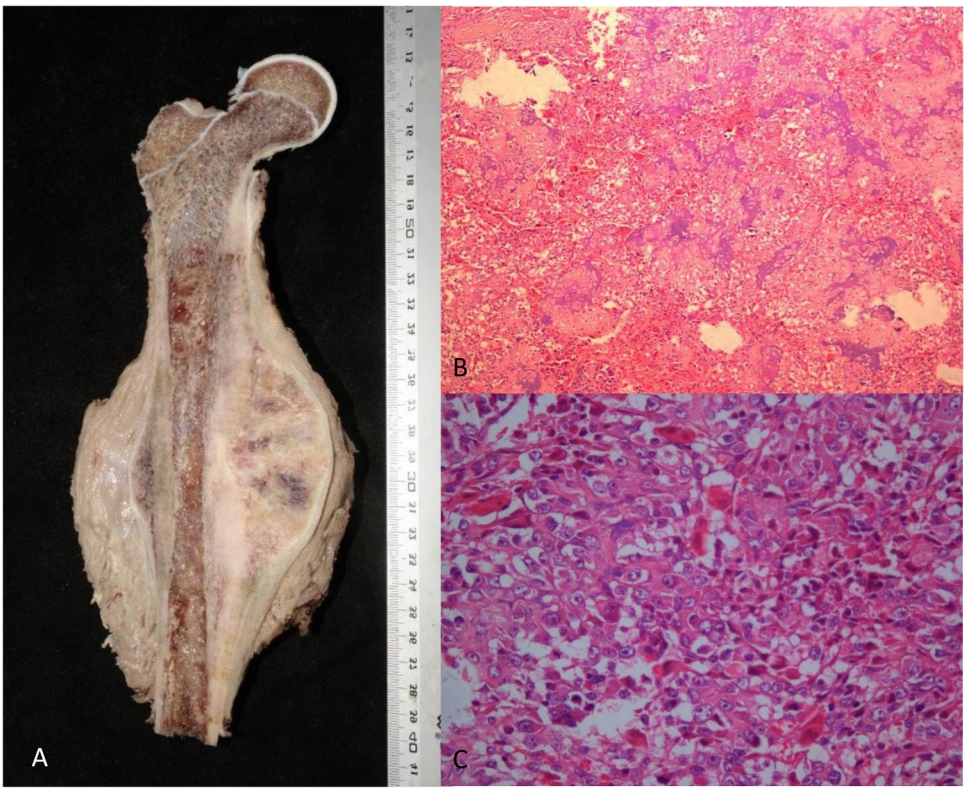

Fig. 3. a, Macroscopic section of the specimen, coronal plane; b and c, low- (X40) and high-power (X100) of the histological view of the high-grade surface osteosarcoma.

Table 1
Clinical features, treatment, outcome and follow-up of 20 patients with high-grade surface osteosarcoma

	Age Gender	Localization	Surgery	Surgical margins	Surgical Staging (MSTS)	Chemotherapy	Outcome	FU months	Recurrence,months
1	15/M	Femur proximal	Resection	Marginal	III (Lung)	Neoadjuvant	DOD	24	LR, 13
2	14/M	Femur diaphysis	Resection	Wide	IIB	Neoadjuvant	CDF	182	
3	19/F	Tibia proximal	Resection	Marginal	IIB	Adjuvant	DOD	35	Lung,35
4	33/M	Femur distal	Amputation	Wide	IIB	Adjuvant	DOD	104	Bone,76
5	21/M	Tibia diaphysis	Resection	Wide	IIB	Adjuvant	CDF	154	
6	18/M	Femur diaphysis	Resection	Marginal	IIB	Adjuvant	DOD	72	Lung,72
7	26/M	Femur distal	Amputation	Wide	IIB	Adjuvant	DOD	36	Lung,30
8	25/M	Femur distal	Resection	Wide	IIB	Adjuvant	CDF	117	
9	15/M	Femur diaphysis	Resection	Wide	IIB	Neoadjuvant	DOD	42	Lung,36
10	40/M	Tibia proximal	Resection	Wide	IIB	Adjuvant	DOD	5	Lung,4
11	27/M	Tibia diaphysis	Resection	Marginal	IIB	Adjuvant	DOD	48	Lung,32
12	26/F	Tibia proximal	Amputation	Wide	IIB	Neoadjuvant	DOD	38	Lung,30
13	16/M	Femur distal	Resection	Wide	IIB	Neoadjuvant	NED	30	Lung,5
14	19/F	Femur distal	Resection	Wide	IIB	Adjuvant	DOD	39	Lung,19
15	43/F	Femur diaphysis	Resection	Marginal	IIB	Adjuvant	DOD	14	Local + Lung,13
16	24/F	Femur distal	Resection	Wide	IIB	Adjuvant	CDF	36	
17	57/M	Femur distal	Resection	Wide	IIB	Adjuvant	CDF	37	
18	17/M	Tibia diaphysis	Resection	Wide	IIB	Neoadjuvant	CDF	31	
19	46/M	Femur distal	Resection	Wide	IIB	Adjuvant	NED	27	Lung,24
20	27/M	Fibular distal	Amputation	Wide	III (Lung)	Adjuvant	DOD	10	

Bone, bone metastasis; CDF, continue disease-free; DOD, dead of disease; F, female; FU, follow-up; LR, local recurrence; Lung, lung metastasis; M, male; NED, no evidence of disease.

months in two patients who had initially undergone resections with marginal margins. There was no local recurrence in the patients who tumors had been resected with wide margins. The local recurrence rates for wide and marginal margins were 0% and 40%, respectively. Thirteen of these patients developed lung metastasis, and one patient developed cervical spine metastasis. Twelve patients died of metastasis and the other two patients were still alive after resection of the lung metastasis. The total local recurrence rate was 10% (2/20) and the distant metastasis rate was 70% (14/20).

Survival analysis

The 3- and 5-year overall survival probability estimates were 67.7% and 37.6%, respectively (Fig. 4). On comparison of survival between subgroups, no significant difference in overall survival was found when age, gender, anatomic location (diaphysis or metaphysis), marrow involvement of the lesion, surgical margin and the use of neoadjuvant chemotherapy were evaluated as independent variables. Lung metastasis at presentation (stage III) was associated with a worse overall survival ($P < 0.01$) when compared with stage IIb cases. Distant metastasis was associated with a worse overall survival ($P < 0.01$) when compared with localized disease. In the 18 patients who presented without metastasis, no difference in survival was noted in patients who received neoadjuvant and adjuvant chemotherapy when compared with those who received adjuvant chemotherapy only ($p = 0.94$) (Fig. 5).

Discussion

High-grade surface osteosarcoma has the worst outcome of the three subtypes of surface osteosarcoma [8,10]. The other two subtypes, parosteal osteosarcoma and periosteal osteosarcoma, have better outcomes than conventional intramedullary osteosarcoma when wide surgical margins are achieved. The inclusion criteria in our study was osteosarcoma arising on the surface of bone and where high-grade osteosarcoma was present histologically, while dedifferentiated parosteal osteosarcoma and periosteal osteosarcoma were excluded. In our study, all the radiological and pathological analysis were performed in our hospital. Pathologist reviewed all the gross specimen photos and microscopic slides to exclude the dedifferentiated parosteal osteosarcoma and periosteal osteosarcoma. The study by Okada [8] included 46 patients from the files of the Mayo Clinic, and approximately half of the patients were managed with a combination of surgery and systemic chemotherapy. Follow-up information was available for 35 patients, and the 5-year overall survival rate was 46%. According to the authors, wide surgical margins were essential for local control and chemotherapy improved the outcome for patients with high-grade surface osteosarcoma. In the study by Staals [10], the 5-year survival rate was 82%; patients with metastasis and limb sacrifice surgery had worse outcomes. In Nouri's study [11], the author reported four cases of high grade surface osteosarcoma, three in four died of disease at the end of follow-up. The 5 years survival of high grade tumors (4 high grade surface osteosarcomas and 6 dedifferentiated parosteal osteosarcomas) was 35.4%. In our study, the 5-year survival rate was 37.6%. This was lower than that in the study by Okada [8]. Compared to patients with conventional osteosarcoma treated in our center, the survival rate was much lower [12], because of the higher metastasis rate (70%) in high-grade surface osteosarcoma, with the use of the same chemotherapy regimen for both patient groups. In patients with conventional osteosarcoma, both pre- and postoperative chemotherapy were administered for limb salvage patients; in our series, 6 patients received both pre- and postoperative chemotherapy, 14 patients received only postoperative chemotherapy. But we cannot find significant difference in metastasis free survival in two chemo groups, according to the small case number.

In our study the ages ranged from 14 to 57 years, and the median age was 24 years, which is similar to previous reports. All the tumors involved the lower limb, consistent with the report by Staals [10]. Although some studies report high-grade surface osteosarcoma of the upper limb [6-8], the lower limb is more commonly involved.

On imaging, the tumor characteristically arises from the surface of the bone and aggressive features with ossification. The histopathologic findings can differentiate this tumor from parosteal osteosarcoma because the microscopic findings differ, with parosteal osteosarcoma having a fibroblastic appearance. When chondroid is readily apparent, and the tumor appear chondroblastic, periosteal osteosarcoma should be ruled out. The diagnosis of high-grade surface osteosarcoma, just as with other bone sarcomas, should be based on clinical, radiological, and pathological examination.

In our series, the local recurrence rate was 10% (2/20). A wide surgical margin is essential for local control of the tumor; our study showed the same result. For marginal margins, the local recurrence rate was 40% (2/5), which is higher than the acceptance rate for limb salvage surgery. Wide margins are essential for resecting this highly

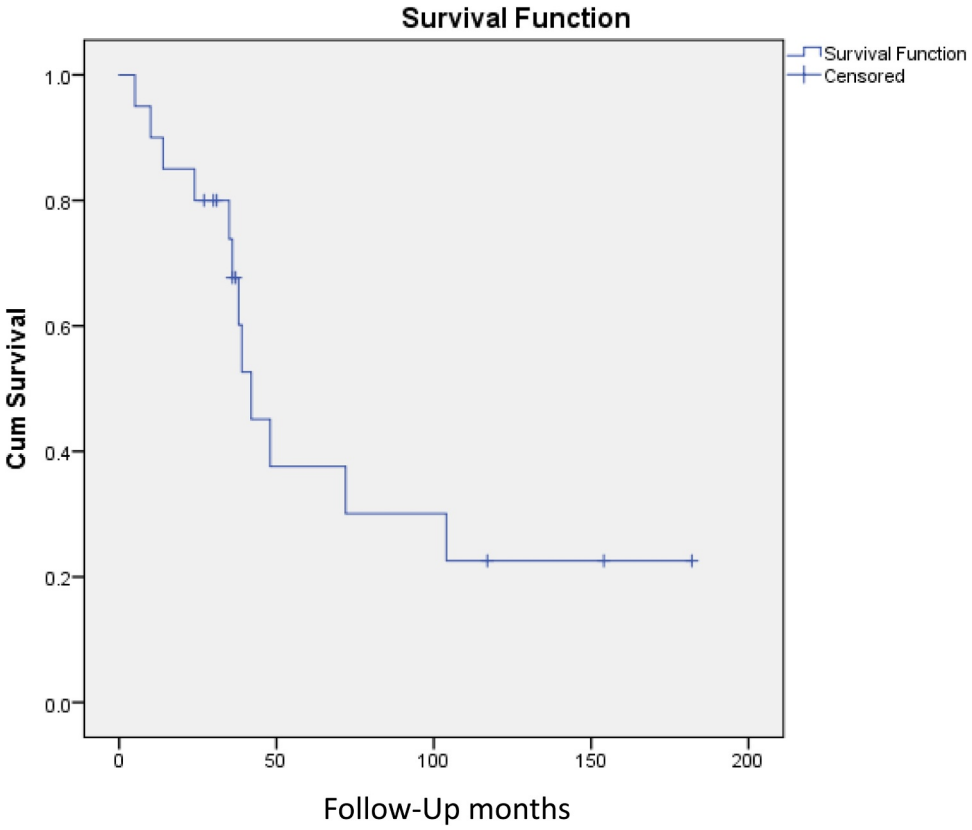

Fig. 4. Kaplan–Meier overall survival curve of the 20 patients with high-grade surface osteosarcoma.

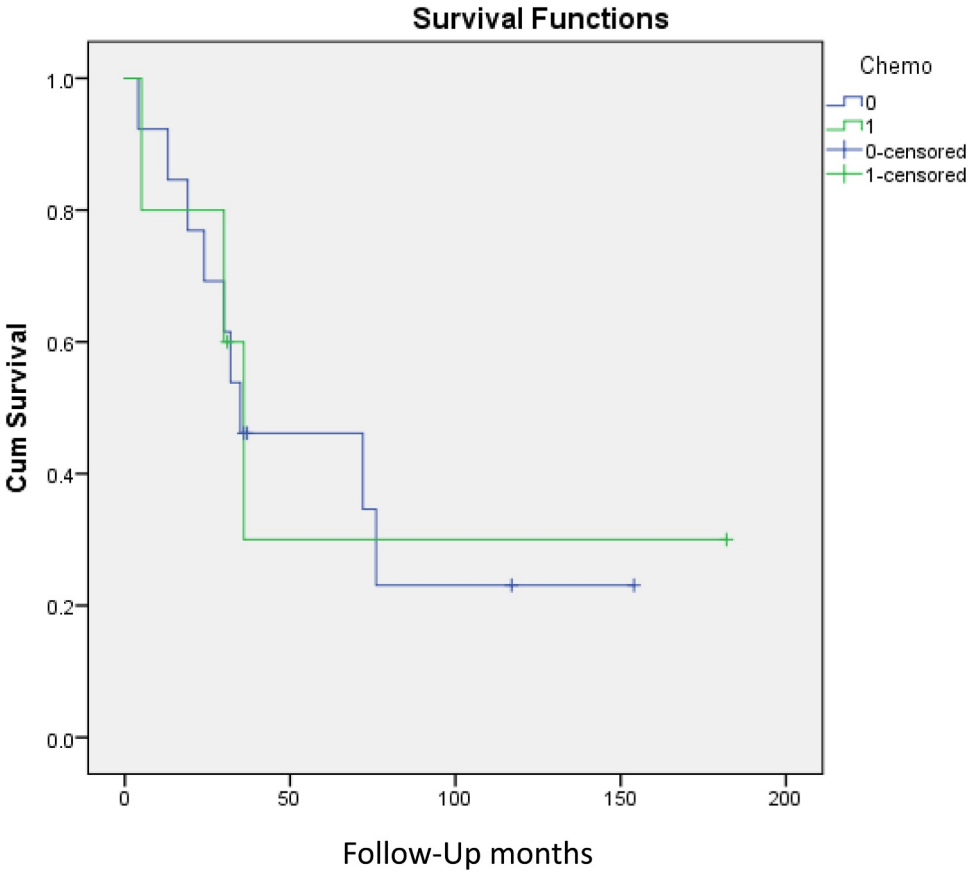

Fig. 5. Kaplan–Meier metastasis-free survival curve of the 18 patients in stage IIb with high-grade surface osteosarcoma. 1, both neoadjuvant and adjuvant chemotherapy; 0, adjuvant chemotherapy only.

malignant tumor. In some patients, the soft tissue mass is very large and close to the neurovascular bundle. Preservation of the neurovascular bundle necessitates a marginal margin on the neurovascular bundle for limb salvage, which may increase the risk of local recurrence.

Distant metastasis has significant adverse impact in the survival in high-grade surface osteosarcoma. In the study by Staals [10], six patients developed distant metastasis and 3 of them died of disease. In our study, the mortality was even higher; 12 of 14 patients with distant metastasis died of the disease. The high metastasis rate plays a role in the poor survival. Improvement in chemotherapy and in the treatment of metastatic lesions are critical in the control of this rare disease.

Our study has limitations. Firstly, the study period spanned 23 years from 1992 through 2015. In those 23 years, imaging modalities and surgical technology have evolved. We thus included only the cases after 2000 for survival analysis. Secondly, the sample size for survival analysis was small; inclusion of more patients is however difficult in a single institution study of a rare disease.

In conclusion, our study shows that high-grade surface osteosarcoma still has a poor survival rate despite contemporary management techniques. The high metastasis rate is the leading cause for poor survival. Investigations into improving chemotherapy is crucial for this disease.

CRediT authorship contribution statement

Zhiping Deng: Conceptualization, Methodology, Software, Writing - original draft, Funding acquisition. **Zhen Huang:** Data curation, Methodology. **Yi Ding:** Data curation, Methodology, Writing - original draft. **Yongbin Su:** Data curation, Methodology, Writing - original draft. **Chung Ming Chan:** Data curation, Writing - review & editing. **Xiaohui Niu:** Conceptualization, Supervision, Writing - review & editing, Funding acquisition.

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Conflicts of interest

There are no conflicts of interest.

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