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ORIGINAL ARTICLE

Prognostic implication of adjuvant/neoadjuvant chemotherapy consisting of doxorubicin and ifosfamide in patients with extraskeletal osteosarcoma

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Abstract

Background Extraskeletal osteosarcoma (ESOS) is an extremely rare soft tissue sarcoma. Their prognosis remains poor. Our purposes were to identify the effective chemotherapeutic regimen for ESOS.

Methods We retrospectively reviewed 16 patients with ESOS treated at the Osaka University Orthopaedic Oncology Group between 1992 and 2012. We extracted the clinical data on patients. Kaplan–Meier method and the log-rank test were used for survival analyses.

Results Median age of the patients was 61.5 years (range 25–79 years). Wide local excision was performed for 11 patients and 9 patients were treated combined with chemotherapy. The 5-year disease-specific survival (DSS) rate was 53.9%. The 5-year DSS rates for patients treated with adjuvant/neoadjuvant chemotherapy or not were 66.7% or 25%, respectively ($p=0.0215$). Furthermore, the 5-year DSS rates for patients treated with adjuvant/neoadjuvant chemotherapy consisting of doxorubicin and ifosfamide and those treated with other regimens were 100% or 40%, respectively ($p=0.0327$).

Conclusion The present study demonstrated that adjuvant/neoadjuvant chemotherapy, especially consisting of doxorubicin and ifosfamide, was potentially efficacious for ESOS. Further prospective study using this multimodality treatment approach to patients with ESOS should be strongly warranted.

Keywords Extraskeletal osteosarcoma · Chemotherapy · Doxorubicin · Ifosfamide

Introduction

Extraskeletal osteosarcoma (ESOS) is an aggressive mesenchymal neoplasm that consists of only about 1% of all soft tissue sarcomas [1–5]. This sarcoma mainly affects elderly patients compared to conventional osteosarcoma of bone. While some retrospective studies investigated the effectiveness of therapies including surgery, chemotherapy or radiotherapy for ESOS, adequate multimodality therapy remains uncertain because of conflicting results in previous reports which was mainly associated with their extreme rarity [6–13].

Since the chemotherapy for ESOS was not considered to be effective as well as for other histological types of adult soft tissue sarcomas, adjuvant/neoadjuvant chemotherapy was rarely given for patients with ESOS and very limited studies targeting for the efficacy of chemotherapy on ESOS were reviewed until 2001. After that, one study reported that there was some positive contribution of ifosfamide-based

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chemotherapy for ESOS [6]. However, therapeutic implication of adjuvant/neoadjuvant chemotherapy for patients with ESOS has been still controversial.

The recent preliminary study suggested the advantage of perioperative high-dose doxorubicin (75 mg/m^2) and ifosfamide (10 g/m^2)-based chemotherapy regimen for ESOS [14]. The chemotherapy significantly improved local relapse-free survival as well as radiation therapy, but not disease-specific survival (DSS) [14]. We agreed that doxorubicin and ifosfamide-based chemotherapy could improve the clinical outcome of ESOS patients and hypothesized that our multimodality treatment for ESOS, adjuvant/neoadjuvant chemotherapy consisting of doxorubicin and ifosfamide combined with wide surgical excision, might improve their DSS.

The present study was aimed to retrospectively examine the clinical characteristics and outcome of ESOS patients treated with or without multimodality treatment and compare the efficacy of chemotherapy regimens on ESOS.

Patients and methods

Between 1992 and 2012, 20 patients were diagnosed for ESOS by Osaka University Orthopaedic Oncology Group. We excluded 4 patients in this retrospective study because no treatment was administered. Then, we retrospectively reviewed medical records of the rest of 16 ESOS patients. Within those patients, we found 3 patients whose sarcoma occurred after radiation therapy to treat uterine cancer or Hodgkin's lymphoma, and we distinctively excluded them from the present study because post-radiation osteosarcoma has biologically different characteristics associated with poor prognosis from primary ESOS (patients #13–15, Table 1). Then, the data of 13 primary ESOS patients including their clinicopathological characteristics, definitive surgery, the regimens of chemotherapy and treatment outcome were investigated (Table 1). All cases of ESOS were diagnosed by musculoskeletal pathologists at our institutes based on the criteria of previous description [5]. Histological subtypes were not shown because the pathologists in our institutes do not routinely mention the histological subtypes of ESOS in contrast to those of osteosarcoma originated from bone.

Median age of the patients was 61.5 years (range 25–79 years). The analyzed patients consisted of 8 males and 5 females. Primary tumors were located at the upper extremity in 5 patients, lower extremity in 5 patients, trunk wall in 2 patients and retroperitoneum in 1 patient (Table 2). The median follow-up period was 50.5 months (range 1–140 months). We used AJCC 6th edition cancer staging system. We diagnosed 2 patients with AJCC Stage IIA, 1 patient with Stage IIB, 7 patients with Stage III and 3 patients with Stage IV. Adjuvant/neoadjuvant chemotherapy was administered for 9 patients as follows; combination of doxorubicin (60 mg/m^2) and ifosfamide (10 g/m^2), combination of doxorubicin (70 mg/m^2) and cisplatin (100 mg/m^2), combination of ifosfamide (5 g/m^2), carboplatin (300 mg/m^2) and etoposide (300 mg/m^2) (ICE), high-dose ifosfamide (12–15 g/m^2), combination of epirubicin (80 mg/m^2) and carboplatin (300 mg/m^2) or high-dose methotrexate (8 g/m^2 × 2). We suitably adjusted the dose and cycles of chemotherapy according to the patient's age and adverse effects. Surgical resection was undergone in 12 patients, and their consequent surgical margins were R0 in 11 patients including one amputation and R1 in one patient at the definitive surgery in our institutes (Table 2).

We compared the DSS rate of each group using Kaplan–Meier method and log-rank test for statistical estimate. Disease-specific survival (DSS) was defined as the time from the initial presentation to death associated with the disease or the last follow-up. p values of less than 0.05 were statistically considered significant.

The ethical approval of this study was obtained from institutional review board of Osaka University Hospital.

Results

The 5-year DSS rate of all 13 patients was 53.9% (Fig. 1). For clinical outcome at the final follow-up, 5 patients were in continuous disease-free (CDF) and 8 patients were dead of disease (DOD). The 5-year DSS rates of AJCC Stage II and III patients were 100% and 57.1%, respectively, and none of AJCC Stage IV patients survived more than 10 months ($p = 0.0003$) (Fig. 2). As for the regimens of adjuvant/neoadjuvant chemotherapy, 3 patients received doxorubicin and cisplatin combined with high-dose ifosfamide, which was according to the regimen for conventional osteosarcoma of bone (patients #2, 12, 16), 4 patients received doxorubicin and ifosfamide (patients #3, 4, 5, patient #9 also received chemotherapy of ICE regimen) and 2 other patients compromised with coronary heart disease only received ICE (ifosfamide, carboplatin, and etoposide) regimen (patients #8, 11) (Table 1). The 5-year DSS rate was 66.7% for patients treated with adjuvant/neoadjuvant chemotherapy and 25% for those without chemotherapy. In the present study, adjuvant/neoadjuvant chemotherapy significantly improved their DSS ($p = 0.0215$) (Fig. 3a). Moreover, 4 patients who were given doxorubicin and ifosfamide-based chemotherapy regimen (patient #9 also received ICE regimen) were all alive in CDF. Other regimens of chemotherapy were given in 5 patients and 4 of them were DOD. The 5-year DSS rates were 100% and 40% for the patients treated with doxorubicin and ifosfamide-based regimen and other regimens, respectively ($p = 0.0327$) (Fig. 3b). These results suggested that doxorubicin and ifosfamide-based regimen was superior for ESOS to other regimens of chemotherapy. Furthermore,

Table 1 Summary of clinical data for 16 patients With Extraskeletal Osteosarcoma Treated at Osaka University Orthopaedics Group, 1992–2012

Patient no	Age (years)	Sex	Location	Tumor size (cm)	AJCC stage	Chemotherapy	Response rate	Surgery	Follow-up (months)	Status
1	69	M	Forearm	–	IV	–	No data	Wide re-excision	9	DOD
2	49	F	Shoulder	11	IV	+ (IFMx2, DOX + CDDPx1)	No data	–	8	DOD
3	54	F	Shoulder	6.5	III	+ (DOX + IFMx2)	No data	Wide	138	CDF
4	72	M	Lumbar region	14	III	+ (DOX + IFMx6, IFMx2)	80%	Wide	79	CDF
5	71	F	Thigh	17	III	+ (DOX + IFMx6)	90%	Wide	109	CDF
6	67	M	Lower leg	–	IIA	–	No data	Wide re-excision	64	DOD
7	59	F	Lower leg	–	III	–	No data	Wide	36	DOD
8	67	M	Thigh	12	III	+ (ICEx2)	0–10%	Amputation	12	DOD
9	59	M	Forearm	10	IIB	+ (ICEx2, DOX + IFMx2)	No data	Wide	122	CDF
10	79	F	Retroperitoneum	9	IV	–	No data	Marginal	1	DOD
11	63	M	Thigh	11	III	+ (ICEx2)	50%	Wide	94	DOD
12	60	M	Upper arm	8.5	III	+ (IFMx3, DOX + CDDPx3)	50–80%	Wide	37	DOD
13	58	F	Buttock	15	III	+ (IFMx2, DOXxl)	No data	Wide	66	NED
14	47	M	Chest wall	5	IIB	+ (EPI + CBDCAx2, IFMx2)	No data	Wide	26	DOD
15	61	F	Buttock	6	III	+ (IFMxl, MTXxl, DOX + CDDPx3)	No data	Wide	24	DOD
16	25	M	Chest wall	2	IIA	+ (IFMxl, DOX + CDDPx1)	No data	Wide re-excision	140	CDF

M male, *F* female, *response rate* pathological response (percentage of tumor cell necrosis) after neoadjuvant chemotherapy, *DOX* doxorubicin, *IFM* ifosfamide, *CDDPcis*-diamminedichloride platinum, *ICE* ifosfamide, carboplatin, and etoposide, *EPI* epirubicin, *CBDCA* carboplatin, *MTX* methotrexate, *CDF* continuous disease-free, *NED* no evidence of disease, *DOD* dead of disease

Table 2 Demographic data of 13* patients with primary ESOS

Variable	Number	Percent (%)
Gender		
Male	8	61.5
Female	5	38.5
Primary location		
Lower extremity	5	38.5
Upper extremity	5	38.5
Trunk wall	2	15.4
Retroperitoneum	1	7.7
AJCC stage		
IIA	2	15.4
IIB	1	7.7
III	7	53.8
IV	3	23.1
Surgical resection		
No	1	7.7
Yes	12	92.3
RO	11	84.6
R1	1	7.7
Chemotherapy		
No	4	30.8
Yes	9	69.2
DOX + IFM	5	38.5
Others	4	30.8
Neoadjuvant	4	30.8
Adjuvant	2	15.4
Neoadjuvant + adjuvant	2	15.4
No operation	1	7.7

RO complete resection with negative margins, *R1* removal of all macroscopic disease but with microscopically positive margins, *DOX* doxorubicin, *IFM* ifosfamide

*Three patients with post-radiation ESOS were excluded

DSS curves of the two groups treated with chemotherapy other than doxorubicin and ifosfamide-based regimen or without chemotherapy were similar, suggesting that adjuvant/neoadjuvant chemotherapy other than doxorubicin and ifosfamide-based regimen might have little efficacy in patients with ESOS (Fig. 3c).

We present here 2 representative cases of ESOS treated with adjuvant/neoadjuvant chemotherapy of doxorubicin and ifosfamide reviewed in this study.

Patient #4

The patient was 72-year-old male with a 16 cm mass located at his lumbar region. There were markedly ossified and hemorrhagic changes within the tumor in the CT scan and MRI (Fig. 4a, b). The tumor directly involved into retroperitoneum and displaced the right kidney. No pulmonary metastasis was detected at initial presentation. Open biopsy was performed at another hospital, and then referred to our hospital as a malignant soft tissue tumor suspicious of ESOS. The final diagnosis was confirmed ESOS after histopathological review by our sarcoma-specializing pathologists, and staged AJCC clinical stage III based on the criteria. We treated him with 4 cycles of neoadjuvant chemotherapy, consisting of doxorubicin (70 mg/m^2 × 4) and ifosfamide (9 g/m^2 × 4). The tumor was then resected with wide surgical margin (Fig. 4c, d). The histopathological findings of resected specimen showed massive tumor cell necrosis with heavy reactive ossification after neoadjuvant chemotherapy, and the histological response rate (tumor necrosis rate) was estimated as 80% (Fig. 4e). He was further treated with 4 cycles of adjuvant chemotherapy; 2 cycles of doxorubicin (60–70 mg/m^2) and ifosfamide (9 g/m^2 × 2) and 2 cycles of high-dose ifosfamide (12 g/m^2 × 2). After 79 months postoperatively, his oncological status was CDF.

Patient #5

The patient was 71-year-old female with a 17 cm mass located at her left anteromedial thigh. There were heavily ossified and hemorrhagic changes within the tumor in plain X-ray and MRI (Fig. 5a, b). Femoral artery and vein were involved within the tumor. No pulmonary metastasis was detected at presentation. Open biopsy was performed at another hospital, and she was referred to our hospital diagnosed as high-grade pleomorphic sarcoma (Fig. 5c). Histopathological review by our sarcoma specialists confirmed the diagnosis of ESOS with AJCC Stage III based on the criteria. We treated her with 2 cycles of neoadjuvant chemotherapy consisting of doxorubicin (60 mg/m^2 × 2) and ifosfamide (8 g/m^2 × 2). The tumor was then surgically resected with wide margin (Fig. 5d). The femoral artery and vein were resected together with the tumor and reconstructed with synthetic blood vessels. In the resected specimen, only scattered viable tumor cells were detected after neoadjuvant chemotherapy, and the histological response rate was estimated as 90% tumor necrosis (Fig. 5e, f). After the surgery, 4 cycles of adjuvant chemotherapy, doxorubicin (60 mg/m^2 × 4) and ifosfamide (8 g/m^2 × 1, 7 g/m^2 × 3), were given. After 109 months postoperatively, her oncological status was CDF.

Discussion

The present study demonstrated that our multimodality treatment for patients with ESOS, i.e., doxorubicin and ifosfamide-based adjuvant/neoadjuvant chemotherapy combined with wide surgical excision, improved their DSS and

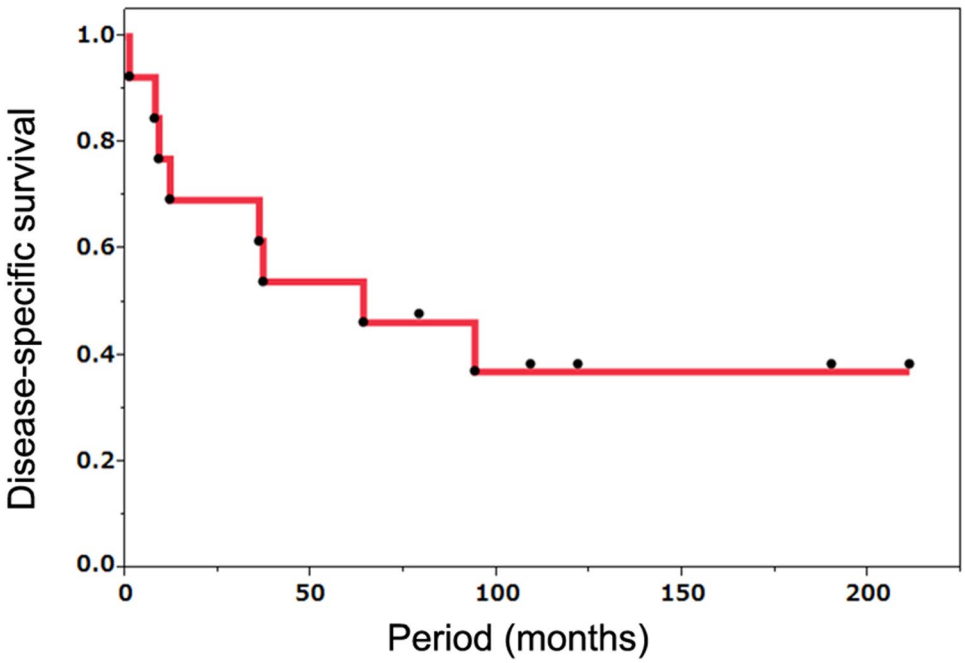

Fig. 1 Disease-specific survival (DSS) of all 13 patients is shown. 5-year DSS rate was 50%

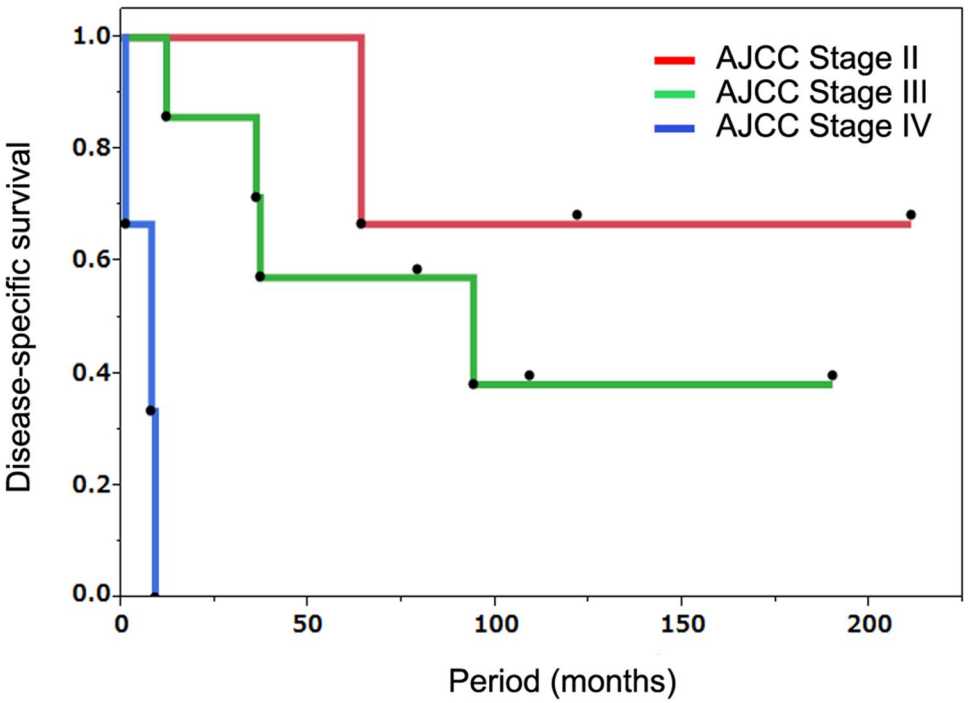

Fig. 2 DSS of patients between AJCC stages is shown. The 5-year DSS rate was 100% in AJCC Stage II patients, 57.1% in AJCC Stage III and 0% in AJCC Stage IV patients (log-rank test, $p = 0.0003$)

chemotherapy regimen of doxorubicin and ifosfamide might be superior to other chemotherapy regimens for ESOS.

Extraskeletal osteosarcoma is basically categorized as a high-grade histological type of soft tissue sarcoma with poor prognosis [1–5]. The role of adjuvant/neoadjuvant chemotherapy for ESOS has been still controversial [6–13]. The discrepancy of those results was considered mainly due to extreme rarity of ESOS and was also probably associated with heterogeneity of their chemotherapeutic regimens and dose intensities. However, recent several reports have suggested the potentially prognostic efficacy of chemotherapy for patients with ESOS [14–17]. As for chemotherapeutic regimens, whether ESOS should be treated with adjuvant/neoadjuvant chemotherapy according to the regimen for high-grade soft tissue sarcoma or conventional osteosarcoma of bone still remains uncertain because ESOS is originated

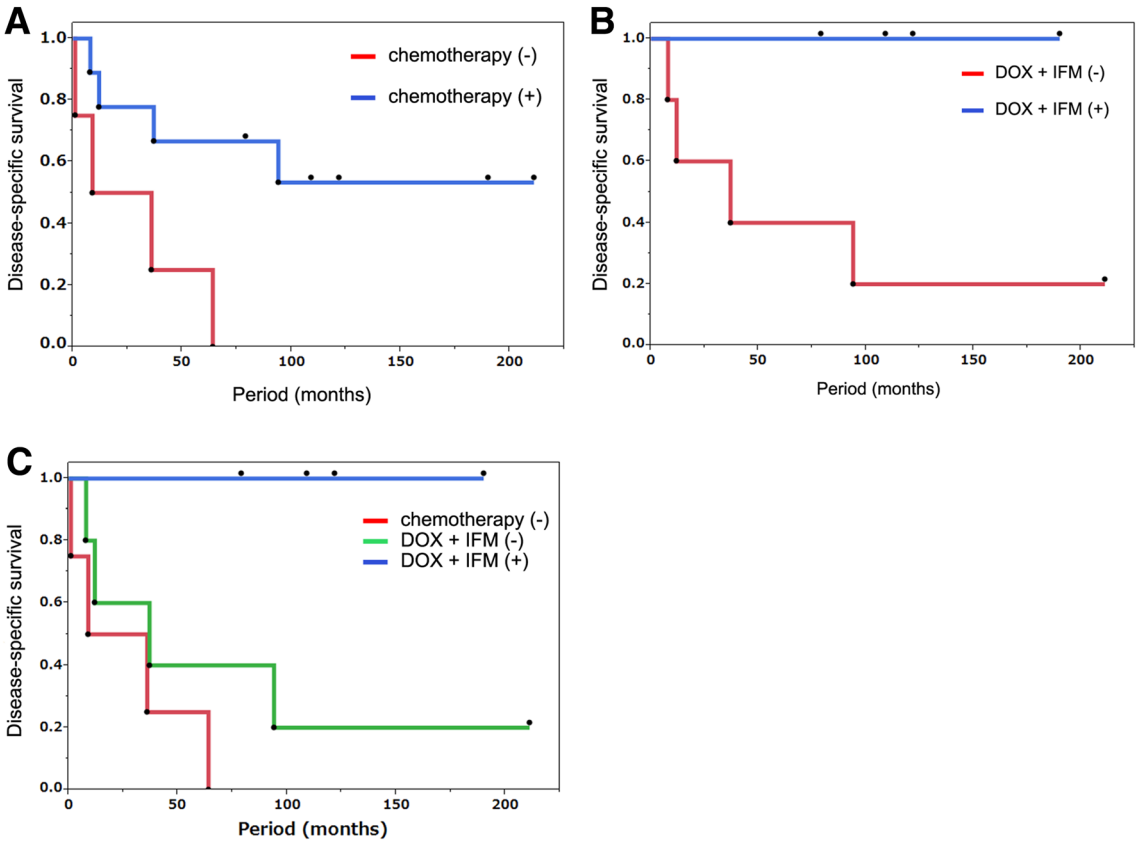

Fig. 3 **a** DSS of patients with or without adjuvant/neoadjuvant chemotherapy is shown. The 5-year DSS rate was 66.7% for patients treated with chemotherapy and 25% for patients without chemotherapy (log-rank test, $p=0.0215$). **b** 5-year DSS rate was 100% for patients treated with chemotherapy of doxorubicin and ifosfamide, and 40% for patients treated with chemotherapy of other regimens (log-rank test, $p=0.0327$). **c** DSS of patients with chemotherapy with regimens other than doxorubicin and ifosfamide or without chemotherapy is shown. We also showed DSS of patients treated with chemotherapy of doxorubicin and ifosfamide-based regimen

from soft tissue but has similar histopathological characteristics to osteosarcoma of bone [2, 8, 14]. Some studies suggested a superiority of osteosarcoma-type chemotherapy regimen including doxorubicin, ifosfamide and cisplatin than soft tissue sarcoma-type regimen (doxorubicin with/or without ifosfamide) [15, 17], but another study suggested the efficacy of doxorubicin-based or doxorubicin and ifosfamide-based chemotherapy regimen for ESOS patients according to soft tissue sarcoma [14, 16]. We also favored soft tissue sarcoma-type of doxorubicin and ifosfamide-based adjuvant/neoadjuvant chemotherapy because of the difficult applicability to use conventional osteosarcoma-type chemotherapy (doxorubicin, cisplatin, high-dose methotrexate with/or without ifosfamide) for ESOS patients due to their elderly age compared with younger age in conventional osteosarcoma of bone [2, 5]. Longhi et al. indicated higher survival in patients who received perioperative chemotherapy with a trend in favor of multiagent osteosarcoma-type regimen including doxorubicin, ifosfamide, and cisplatin [15]; however, both regimens of osteosarcoma-type and soft tissue sarcoma-type included doxorubicin and ifosfamide, suggesting their own efficacy on ESOS possibly depending on their doses. Torigoe et al. reported that chemotherapy did not significantly improve the prognosis of ESOS patients [13]. In their study, 15 patients received chemotherapy and 4 of them received the regimen including doxorubicin and ifosfamide. But interestingly, based on their data, all 4 patients treated with doxorubicin and ifosfamide were alive at the period of their investigation.

Several investigators have previously showed that AJCC stage affects local recurrence and/or survival as well as patients' age, primary tumor size, tumor depth and surgical margin and that wide surgical excision combined with/or without perioperative chemotherapy for ESOS improved the clinical outcome [11, 12, 15]. Fan et al. demonstrated that AJCC stage, which depends on tumor size, was the strongest predictor for local relapse-free survival [14]. In agreement with previous studies, the prognosis of AJCC Stage IV patients was very poor compared to AJCC Stage II or III patients [11–14]. Moreover, chemotherapy, especially doxorubicin and ifosfamide-based regimen, was an important predictor for local relapse-free survival [6, 13, 14]. In addition,

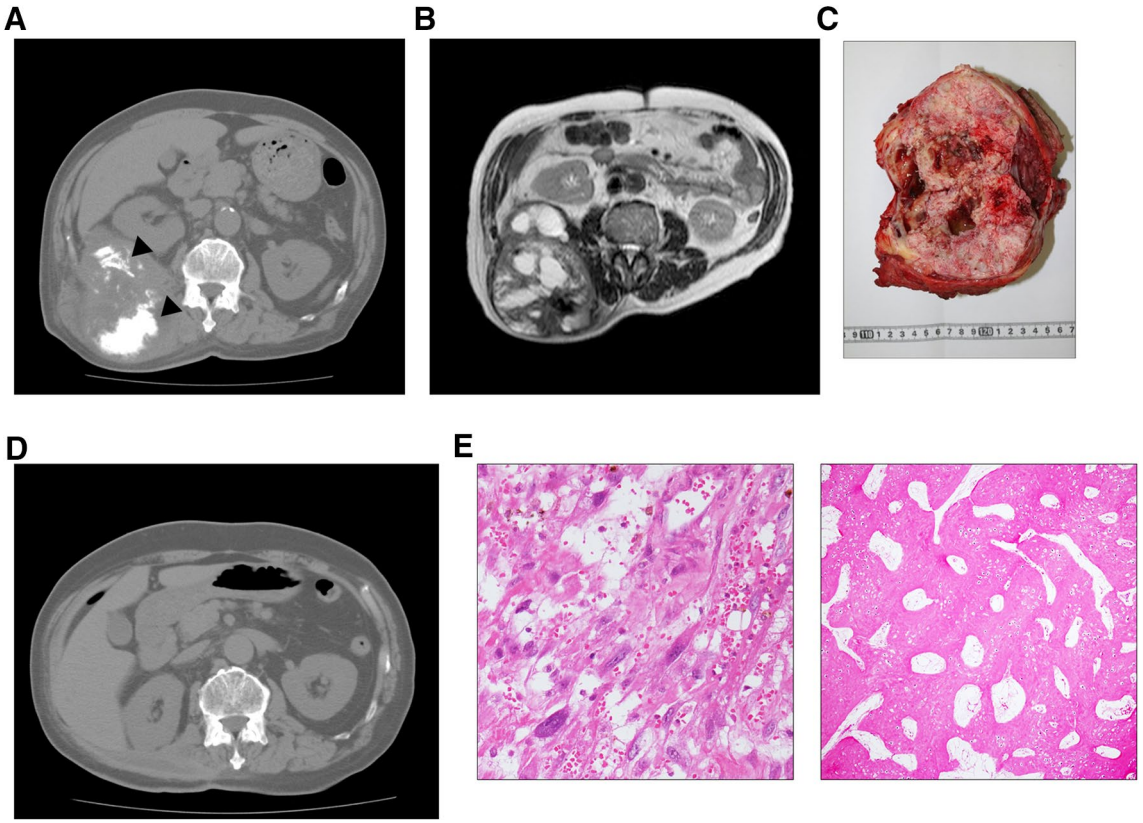

Fig. 4 Patient #4: 72 year-old male. **a** Computed tomography (CT) image of extraskeletal osteosarcoma located at his right lumbar region before neoadjuvant chemotherapy. There was a large soft tissue mass with multiple areas of ossification (arrow heads). **b** Tumor image of T2-weighted magnetic resonance imaging (MRI) is shown. **c** Macroscopic findings of surgically resected specimen are shown. **d** CT image of extraskeletal osteosarcoma located at the lumbar region after surgery. **e** Histopathological images of the tumor after neoadjuvant chemotherapy was presented. Histological response was estimated as 80% of tumor necrosis

chemotherapy tended to improve DSS [14]. In accordance with those previous studies, our current findings indicated that the prognosis was significantly different between AJCC Stage II and III or IV and that the significant improvement in DSS was observed between the treatment group with and without adjuvant/neoadjuvant chemotherapy combined with wide surgical excision. These prognostic factors were all the same in patients with soft tissue sarcomas other than ESOS, thus adjuvant/neoadjuvant chemotherapy consisting of doxorubicin and ifosfamide might be well indicated for relatively younger (less than 65 or 70 years old) patients with high-grade, large (more than 5 cm in maximal diameter) and localized, i.e., AJCC stage III, ESOS as well as for those with other high-grade, large and localized soft tissue sarcomas. Indeed, Fan et.al. reported that they administered chemotherapy for tumors greater than 5 cm in patients younger than 60 years [14].

Several previous studies investigated the efficacy of radiation therapy for ESOS [14, 15]. They demonstrated that radiation therapy improved relapse-free survival or tended to improve the overall survival. Therefore, radiation therapy may be a candidate for treatment in ESOS. In the present study, only one patient received radiation therapy, so we have little evidence to analyze the efficacy of radiation therapy for ESOS.

The present study was associated with several limitations. First, our investigation was retrospective and single-group study. Therefore, we could not fully eliminate the unintentional bias in the selection of patients. Second, the number of ESOS patients in the present series was small, because ESOS is an extremely rare soft tissue sarcoma. Therefore, to confirm the evidence of efficacy of chemotherapy, especially including doxorubicin and ifosfamide, for ESOS, prospective research in a larger trial conducted by multi-centers is needed.

In conclusion, we herein demonstrated that multimodality treatment of adjuvant/neoadjuvant chemotherapy combined with wide surgical excision could improve the prognosis of patients with ESOS, and suggested the chemotherapeutic regimen of doxorubicin and ifosfamide was superior to other regimens for ESOS. We propose ESOS

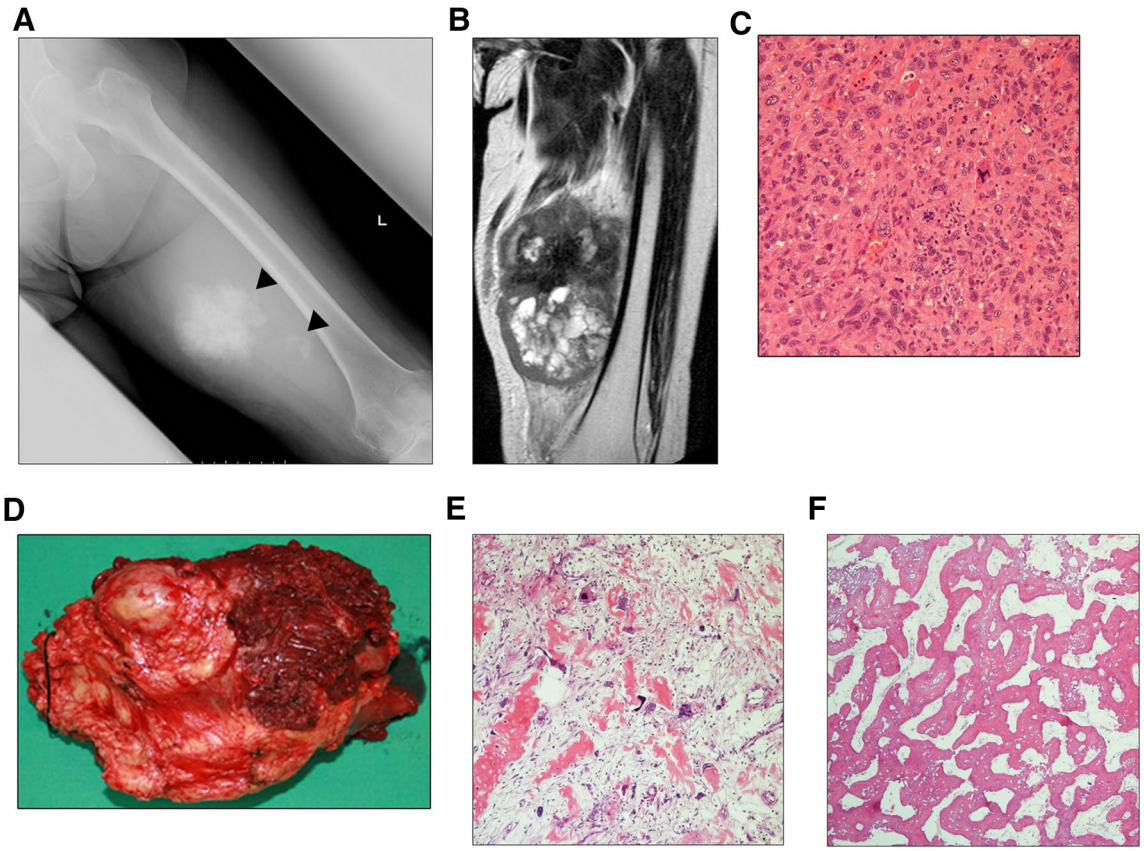

Fig. 5 Patient #5: 71 year-old female. **a** Plain X-ray of extraskeletal osteosarcoma located at the left anteromedial thigh before surgery. There was a large soft tissue mass with multiple areas of ossification (arrow heads). **b** Tumor image of T2-weighted magnetic resonance imaging (MRI) is shown. **c** Histopathological findings of open biopsy specimen showing sheet-like proliferation of undifferentiated atypical oval and short spindle-shaped tumor cells with numerous mitotic counts. **d** Macroscopic resected specimen is shown. **e**, **f** Histopathological images of resected tumor specimen after neoadjuvant chemotherapy is presented. Histological response was estimated as 90% of tumor necrosis

should be treated with doxorubicin and ifosfamide-based adjuvant/neoadjuvant chemotherapy as same as for other high-grade soft tissue sarcomas rather than for conventional osteosarcoma of bone mainly affecting adolescent and young adult patients.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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