Journal of Surgical Oncology 2016;114:495–500

Forty-Eight Cases of Leiomyosarcoma of Bone in Japan: A Multicenter Study From the Japanese Musculoskeletal Oncology Group

TOMOAKI MORI, MD, PhD,[1,2] ROBERT NAKAYAMA, MD, PhD,[1]* MAKOTO ENDO, MD, PhD,[3] HIROAKI HIRAGA, MD, PhD,[4] MASATO TOMITA, MD, PhD,[5] NAOMASA FUKASE, MD, PhD,[6] EISUKE KOBAYASHI, MD,PhD,[2] AKIRA KAWAI, MD, PhD,[2] TAKAFUMI UEDA, MD, PhD,[7] AND HIDEO MORIOKA, MD, PhD[1]

[1]Department of Orthopaedic Surgery, School of Medicine, Keio University, Tokyo, Japan
[2]Division of Musculoskeletal Oncology, National Cancer Center Hospital, Tokyo, Japan
[3]Department of Orthopaedic Surgery, Kyushu University, Fukuoka, Japan
[4]Department of Orthopaedic Surgery, Hokkaido Cancer Center, Hokkaido, Japan
[5]Department of Orthopaedic Surgery, Nagasaki University, Nagasaki, Japan
[6]Department of Orthopaedic Surgery, Hyogo Cancer Center, Akashi, Japan
[7]Department of Orthopaedic Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan

Background: Leiomyosarcoma of bone (LMSoB) is a rare malignant bone tumor. This multicenter retrospective study was conducted to investigate the diagnosis and the clinical outcome of primary LMSoB in Japan.
Methods: Forty-eight patients (average age: 52 years [range 14–88 years]) with primary LMSoB who were treated at registered institutes in Japan between 1991 and 2014 were recruited. The median follow-up period was 44 months (range: 2–273).
Results: The 5-year overall survival rates and disease-free survival rates were 78.3% and 44.9%, respectively. Surgical treatment was performed in 42 patients, and R0 resection was achieved in 31 patients. Neoadjuvant chemotherapy was administered in 18 patients. The most common regimen (cisplatin-based chemotherapy) was administered in 15 patients, however, no patient achieved a good response in both radiological and histological evaluations. The presence of metastasis at the first visit and a lack of definitive surgery were significantly correlated with poor overall survival, and the surgical margin was a significant prognostic factor for disease-free survival.
Conclusions: This study is the largest LMSoB case series ever reported. Surgical treatment with wide margins was the only treatment that proved to be effective, whereas adjuvant chemotherapy in the present setting did not improve the overall survival.
J. Surg. Oncol. 2016;114:495–500.

KEY WORDS: leiomyosarcoma of bone; prognostic factors; surgery; chemotherapy; cisplatin

INTRODUCTION

Leiomyosarcoma (LMS) is defined as a malignant neoplasm with clear evidence of smooth muscle differentiation on histological, immunohistochemical, or ultrastructural examination. LMS is classified into three entities based on the prognosis and clinical behavior: cutaneous LMS, gastrointestinal and uterine LMS, and somatic LMS [1]. In most cases, somatic LMS occurs primarily in the retroperitoneum, the soft tissue of the extremities, the blood vessels, or rarely, in the bone [1]. Since Evans and Sanerkin reported the first case in 1965 [2], about 130 cases of primary LMS of bone (LMSoB) have been reported, mostly in the form of small case reports [3–5] that have focused on its histological diagnosis. Recently, LMSoB has increasingly been diagnosed as it has gradually gained recognition and as advances in immunohistochemistry have made its diagnosis more accurate [3,4,6,7]. Still, it is difficult to make an accurate diagnosis of LMSoB by biopsy due to the limitations of the histological diagnosis of minute samples from highly heterogeneous primary malignant bone tumors. Moreover, the treatment and prognosis of LMSoB have not been deeply assessed in the literature [8–10] because of its rarity and due to the difficulty in obtaining a histological diagnosis prior to treatment. Although a few studies have addressed the significance of wide resection, the efficacy of chemotherapy and radiotherapy has not been clarified [3,4,11]. On the other hand, several new chemotherapy regimens have been demonstrated to be effective for other types of LMS, including gemcitabine plus docetaxel, trabectedin, and eribulin [12–15]. Based on the fact that LMSoB shares the same pathological characteristics as LMS arising from other tissues, LMSoB may be treated more effectively by the same protocol as other types of LMS. To provide a new insight into the diagnosis and treatment of LMSoB, we performed a multicenter retrospective study of patients with LMSoB who were treated in Japanese Musculoskeletal Oncology Group (JMOG) institutes and analyzed 48 cases to evaluate the clinical outcomes of the patients as well as the diagnosis and treatment of LMSoB. This is the largest study of LMSoB patients ever reported.

PATIENTS AND METHODS

Patients

A total of 48 LMSoB patients who were treated with surgery, chemotherapy, or radiation therapy at 32 JMOG institutes between 1991

Conflict of interest: The authors declare no conflicts of interest in association with the present study.

*Correspondence to: Robert Nakayama, MD, PhD, Department of Orthopaedic Surgery, School of Medicine, Keio University, 35 Shinano-machi, Shinjuku-ku, Tokyo 160-8582, Japan. Fax: +81-3-3353-6597. E-mail: robnak@hotmail.com

Received 27 December 2015; Accepted 20 May 2016

DOI 10.1002/jso.24322

Published online 15 June 2016 in Wiley Online Library (wileyonlinelibrary.com).

and 2014 were assessed in this study. In each case, the histological diagnosis was reviewed and confirmed by individual pathologists of the institution before registration in the present study. Patients with an extraskeletal primary site of LMS and those with a history of prior radiation exposure were excluded from the study. Information on the clinical features of the patients, including sex, age at the first visit, the location of the primary site, tumor size (maximum extent determined by imaging), the American Joint Committee on Cancer (AJCC) staging [16] and the Enneking surgical staging [17], and the presence or absence of metastasis at the time of the diagnosis were collected. The treatment-related factors including the type of local therapy, chemotherapy status, local and distant relapse, the follow-up period, and the outcome were also analyzed. Additional information, such as the results of immunohistochemical staining, the surgical margin in the patients who had surgery, the radiological evaluation (RECIST1.1) [18], and the histological evaluation according to the criteria for osteosarcoma (Rosen Huvos criteria) [19] in the patients who underwent chemotherapy, were also obtained. The duration of overall survival (OS) was defined as the time from the first visit to the date of the last visit to the clinic or death. The duration of disease-free survival (DFS) was defined as the time from the surgery to the date of the last visit to the clinic, death or the date of local recurrence or distant metastasis.

Statistical Analysis

The OS and DFS were estimated using the Kaplan–Meier method and the impact of each prognostic factor was assessed using the log-rank test and Cox's proportional hazards regression method. Variables with a P-value of <0.05 in the univariate or multivariate analyses were considered to be significantly associated with survival. All of the statistical analyses were performed using the JMP 11 software program (SAS Institute Inc., Cary, NC).

RESULTS

Patients Demographics

Forty-eight patients were enrolled in the present study. The characteristics of the patients are shown in Table I. The study population included 19 males and 29 females with an average age of 52 years (range: 14–88 years) at presentation (Suppl Fig. S1). The median follow-up period, excluding the dropouts due to death, was 44 months (range 2–273). The years of each patient's initial visit, which ranged from 1991 to 2014, are shown in Supplementary Figure S2. The sites of the primary lesions were the lower extremities in 37 patients (77.1%) (around the knee, n = 23 [47.9%]), the trunk in 10 patients (20.8%) and the upper extremities in 1 patient (2.1%). The information on the classification of AJCC staging or Enneking surgical staging was available for 35 patients. According to the AJCC staging, 18 patients (51.4%) were classified as stage IIA, 10 (28.6%) as stage IIB, and 7 (20.0%) as stage IV. According to the Enneking surgical staging, eight patients (22.9%) were classified as stage IIA, 20 (57.1%) as stage IIB, and 7 (20.0%) as stage III.

Biopsy and the Initial Diagnosis

A biopsy was conducted prior to treatment in 46 patients. Thirty-five patients (76.1%) received an open biopsy, while 11 patients (23.9%) underwent a core needle biopsy. The diagnosis of LMSoB was confirmed by biopsy in 31 patients (67.4%). The other diagnoses included spindle cell sarcoma (n = 3 [6.5%]), malignant fibrous histiocytoma (MFH)/pleomorphic sarcoma (n = 3 [6.5%]), osteosarcoma (n = 3 [6.5%]), fibrosarcoma (n = 1 [2.2%]) and "other" (n = 5 [10.9%]) (Table II). There was no statistically significant difference in the accuracy rates of open biopsy and needle biopsy in the current study (data not shown). The immunohistological staining information of 39 patients was available. The rates of smooth muscle actin (SMA), muscle actin-specific monoclonal antibody (HHF35) and h-caldesmon positivity were high (Table II).

TABLE I. Demographics of the 48 Patients Enrolled in This Study

	Number	(%)
Sex		
Male	19	39.6
Female	29	60.4
Primary site		
Upper extremity	1	2.1
Lower extremity	37	77.1
Trunk	10	20.8
Primary location of bones		
Femur	24	50.0
Tibia	9	18.7
Pelvis	7	14.6
Talus	2	4.2
Fibula	1	2.1
Calcaneus	1	2.1
Thoracic	1	2.1
Lumbar	1	2.1
Rib	1	2.1
Humerus	1	2.1
Size of tumor (n = 47)		
(mean; 8.3 cm)		
>8 cm	23	48.9
<8 cm	24	51.1
AJCC TNM stage (n = 35)		
IIA	18	51.4
IIB	10	28.6
IV	7	20.0

Surgery and Radiation Therapy

Surgical treatment was performed in 42 patients (87.5%). An adequate safe margin, or R0 (based on the classification of the Union for International Cancer Control [UICC]), was achieved in 31 patients (73.8%). An inadequate margin, or R1 (microscopic residual tumor) and R2 (macroscopic residual tumor), was noted in four patients (9.5%) and six patients (14.3%), respectively; information on the surgical margin was not available for one patient (Table III). Out of the 31 patients in whom an adequate margin was achieved, 24 patients received a limb salvage operation and seven underwent an amputation. Limb salvage operations with endoprostheses were successfully performed in 22 patients, while arthrodesis was performed in two patients. Out of the

TABLE II. Initial Diagnosis at Biopsy and the Results of Immunohistological Staining in Biopsy Specimen

	n	(%)
Initial diagnosis (n = 46)		
Leiomyosarcoma	31	67.4
Spindle cell sarcoma	3	6.5
MFH/pleomorphic sarcoma	3	6.5
Osteosarcoma	3	6.5
Fibrosarcoma	1	2.2
Others[†]	5	10.9
Immunohistological staining		
SMA (n = 32)	31/32	96.9
Desmin (n = 29)	16/29	55.2
HHF35 (n = 16)	14/16	87.5
h-caldesmon (n = 14)	11/14	78.6

HHF35, muscle actin-specific monoclonal antibody clone HHF35; MFH, malignant fibrous histiocytoma; SMA, smooth muscle actin.
[†]Others, non-ossifying fibroma/fibrogenic tumor, giant cell tumor of bone, synovial sarcoma.

TABLE III. Surgical Margins, the Type of Surgical Treament and Local Recurrence

Surgical margin	Type of operation	No. of patients	No. of LR
R0		31	3
	Limb salvage	24	2
	Amputation	7	1
R1		4	1
	Limb salvage	3	1
	Unplanned surgery at other institute	1	0
R2		6	2
	Curettage	5	2
	Unplanned surgery at other institute	1	0
Unknown margin	Limb salvage	1	0
Total		42	6

LR, local recurrence; R0, adequate safe margin with no microscopic residual tumor; R1, inadequate margin with microscopic residual tumor; R2, inadequate margin with macroscopic residual tumor.

four patients with an R1 margin, three received a planned limb salvage operation performed at the JMOG institutes, and one underwent unplanned R1 resection at another institute. Out of the six patients with an R2 margin, five received curettage, and one underwent unplanned surgery at another institute. Regarding additional surgical resection for an inadequate margin, three patients with planned R1 resection did not receive additional local treatment, and one patient with unplanned R1 resection received an additional R0 resection. Six patients with an R2 margin did not receive additional resection. From the viewpoint of surgical planning, we defined definitive surgery as surgery that was performed with the intention of achieving an adequate margin. According to this definition, 35 patients (83.3%) underwent definitive surgery. The other seven patients (16.7%) underwent curettage or unplanned surgery at other institutes.

Radiation therapy was administered in 12 patients. Three patients received radical radiation therapy alone as a local treatment. Three out of six patients with an R2 margin received adjuvant radiation therapy at the initial site of operation, while the other three with an R2 margin and four with an R1 margin did not. Two patients received palliative radiation therapy at the primary site, and four patients received palliative radiation therapy at the sites of metastasis or local recurrence.

Neoadjuvant Chemotherapy

Eighteen patients underwent neoadjuvant chemotherapy. The details of the numbers of patients who received chemotherapy are shown in Table IV. Various neoadjuvant chemotherapy regimens, including cisplatinum-doxorubicin (-methotrexate), ifosfamide-doxorubicin, doxorubicin-dacarbazin-ifosfamide, and gemcitabine-docetaxel, were administered. Among the 18 patients who received neoadjuvant chemotherapy, 15 (83.3%) received a cisplatin-based chemotherapy as the first-line protocol (Table IV). Histological evaluations were available in 13 patients who received neoadjuvant chemotherapy, including 12 patients who received cisplatin-based chemotherapy. One patient fulfilled the criteria of a good grade 3 or 4 responder (according to the Rosen Huvos criteria), while 12 patients were classified as poor grade 1 or 2 responders. Consequently, the histological evaluations of the 12 patients who received cisplatin-based chemotherapy only included 1 good responder (8.3%).

A total of 21 neoadjuvant chemotherapy regimens, including 16 cisplatin-based chemotherapy regimens, were administered to 18 patients, meaning that three patients received two different chemotherapy regimens before surgery. Radiological evaluations were available for 20 of the regimens, which resulted in a partial response (PR) (n = 3), stable disease (SD) (n = 15) and progressive disease (PD) (n = 2). Only 1 of the 16 cisplatin-based chemotherapy regimens was administered to a good responder. In other words, the overall response rate (PR/PR + SD + PD) of the cisplatin based chemotherapy regimens was only 6.3%.

TABLE IV. Neoadjuvant Chemotherapy and the Efficacy of Each Regimen

	n	(%)	RECIST (PR + CR/All) (n = 20)	Rosen Huvos (GrIII + GrIV/All) (n = 13)
Type of chemotherapy (n = 25)				
Neoadjuvant only	3	12.0		
Adjuvant only	7	28.0		
Both neo-/adjuvant	15	60.0		
First-line neoadjuvant chemotherapy regimen (n = 18)				
AP + (IFO, M)	15	83.3		
IA	2	11.1		
MAID	1	5.6		
The efficacy of each neoadjuvant chemotherapy regimen (n = 21)				
AP	5		0/5	0/2
MAP	5		1/5	0/5
AP + IFO	4		0/4	1/4
MAP + IFO	1		0/1	0/1
CDDP	1		0/1	n.a.
IA	2		0/1	n.a.
MAID	1		0/1	n.a.
IE	1		1/1	0/1
GEM/DOC	1		1/1	n.a.

AP, adriamycin-cisplatin; CDDP, cisplatin; IA, ifosfamide-adriamycine; IFO, ifosfamide; IE, ifosfamide-etoposide; GEM/DOC, gemcitabine-docetaxel; MAID, mesna-adriamycin-ifosfamide-dacarbazine; MAP, methotrexate-adriamycin-cisplatin; n.a., not available.

The patient who, according to the radiological evaluation, achieved a PR with cisplatin-based chemotherapy was identified as a poor responder in the histological evaluation. On the other hand, the patient who achieved a grade 3 histological evaluation achieved SD in the radiological evaluation. That is to say, no patients who underwent cisplatin-based neoadjuvant chemotherapy were good responders according to both the radiological and histological evaluations. The 5-year metastasis-free survival rate of 15 patients who underwent cisplatin-based chemotherapy as the first-line protocol was 39.8%. On the other hand, the 5-year metastasis-free survival rate of patients without neoadjuvant chemotherapy was 49.6%. The details of the radiological and histological evaluations for each neoadjuvant chemotherapy regimen are shown in Table IV.

The Outcomes and the Prognostic Factor Analyses

The Kaplan–Meier curves of the OS and DFS are shown in Figure 1. At the latest follow-up of the 48 patients, nine patients had died of the disease, two patients had died of unrelated causes, 10 patients were alive with disease, and 27 patients were alive without evidence of disease. After the initial surgical treatment of the primary site, a total of 14 patients had local recurrence (LR) and/or distant metastasis (DM). LR was observed in six patients, DM was observed in 13 patients, and five patients had both LR and DM. The first site of metastasis was the lung in nine patients. Other sites of initial metastasis were the bone in two patients, skin in one patient, and lymph nodes in one patient. All six patients with LR received surgical treatment for the recurrence. Two patients remain alive without disease while four patients are alive with additional recurrence or DM. Among the 13 patients with DM, 10 patients underwent the surgical resection of the metastatic sites. Four patients died due to metastatic disease; at the time of writing four patients are alive with disease and five patients are alive without disease. The 2-year and 5-year OS rates of all patients were 81.7% and 78.3%, respectively (Fig. 1a). The 2-year and 5-year DFS rates of 37 patients

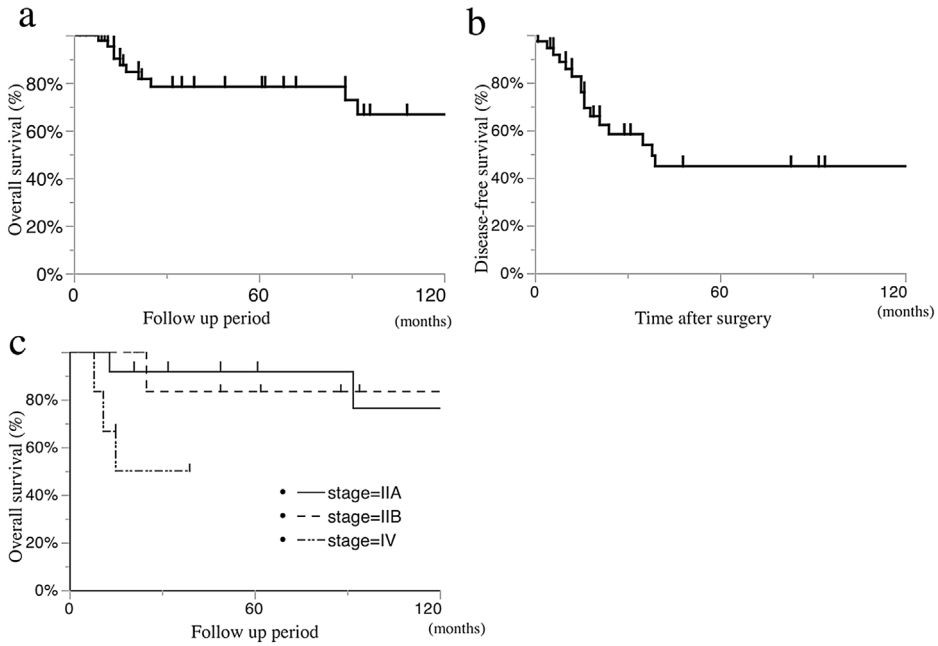

Fig. 1. The overall survival of all patients (**a**), disease-free survival of 37 patients who underwent surgical resection without metastasis at the first visit (**b**), and overall survival of patients in accordance with TNM staging (**c**).

who underwent surgical resection without metastasis at the first visit were 58.3% and 44.9%, respectively (Fig. 1b). The 2-year OS rates in the patients of stage IIA, IIB, and IV (according to the AJCC staging) were 91.7%, 83.3%, and 50.0%, respectively (Fig. 1c). The 2-year OS of stage IV patients was significantly different to that of patients with stage IIA or IIB ($P = 0.0288$, $P = 0.0425$). A univariate analysis was performed to identify potential prognostic factors for OS and DFS (Tables V and VI). The presence of metastasis at the first visit and a lack of definitive surgery were significantly correlated with poor OS ($P = 0.0036$, 0.0355). Among the patients who underwent surgery without metastasis at the first visit, the surgical margin was a significant prognostic factor for DFS ($P = 0.0005$). Although the results suggested

TABLE V. Univariative and Multivariative Analyses Investigating the Prognosis Factor of Overall Survival (n = 48)

			Univariate			Multivariate		
	n	(%)	2-year (%)	5-year (%)	*P*-value	HR	95%CI	*P*-value
Age								
<50	27	56.3	81.8	81.8	0.289			
>50	21	43.8	81.7	74.3				
Sex								
Male	19	39.6	79.8	79.8	0.562			
Female	29	60.4	82.9	77.4				
Site of primary lesions								
Extremity	38	79.2	86.8	82.7	0.0785			
Trunk	10	20.8	61.0	61.0				
Size of tumor								
≧8 cm	23	47.9	85.9	79.7	0.867			
<8 cm	24	50.0	74.7	74.7				
Unknown	1	2.1						
Metastasis at the first visit								
+	7	14.6	50.0	50.0	0.0036	0.28	(0.032–2.54)	0.25
−	41	85.4	87.5	83.8				
Definitive surgery								
+	35	72.9	89.7	85.4	0.0355	3.36	(0.40–21.50)	0.248
−	13	27.1	54.6	54.6				
Surgical margins								
Negative	31	64.6	88.5	83.6	0.779			
Positive	10	20.8	83.3	83.3				
Unknown	1	2.1		n.a.				
No operation	6	12.5		n.a.				
Adjuvant chemotherapy								
+	26	54.2	90.7	85.0	0.589			
−	16	33.3	81.8	81.8				
No operation	6	12.5		n.a.				

HR, hazard ratio; n.a., not available.

TABLE VI. Univariative and Multivariative Analyses Investigating the Prognosis Factor of Disease-Free Survival (n = 37)

			Univariate			Multivariate		
	n	(%)	2-year (%)	5-year (%)	*P*-value	HR	(95%CI)	*P*-value
Age								
<50	24	64.9	60.8	45.6	0.665			
>50	13	35.1	53.9	43.1				
Sex								
Male	15	40.5	62.2	62.2	0.498			
Female	22	59.5	55.7	34.8				
Site of primary lesions								
Extremity	33	89.2	58.9	42.8	0.825			
Trunk	4	10.8	50	50				
Size of tumor								
≧8 cm	19	51.4	69.6	43.5	0.586			
<8 cm	17	45.9	49.6	49.6				
Unknown	1	2.7		n.a.				
Definitive surgery								
+	32	86.5	62.4	52	0.004	2.36	(0.22–22.32)	0.456
−	5	13.5	30	0				
Surgical margins								
Negative	28	75.7	70.8	59	0.0005	7.81	(0.86–56.93)	0.0658
Positive	8	21.6	18.8	0				
Unknown	1	2.7		n.a.				
Adjuvant chemotherapy								
Yes	25	67.6	68.3	54.6	0.07			
No	12	32.4	41.7	27.8				

HR, hazard ratio; n.a., not available.

it might have a potential benefit on the DFS (Table VI, $P = 0.07$), the administration of adjuvant chemotherapy in this study was not a prognosis factor for the OS (Table V, $P = 0.589$).

A multivariate analysis was also performed to determine the factors that were associated with OS and DFS. The surgical margin showed a relatively strong correlation with DFS according to the multivariate analysis ($P = 0.06$), although it did not reach statistically significant difference.

DISCUSSION

In the present study, we analyzed the records of 48 LMSoB patients who were treated at JMOG institutes. The 5-year OS and DFS were 78.3% and 44.9%, respectively. In Adelani's study, the 5-year OS and DFS were reported to be 59% and 41%, respectively [3]. In contrast, the OS in our study was relatively better and there was a considerable gap between OS and DFS. This is because the survival of 14 patients who had LR and/or DM was fairly good. Among them, 10 patients were alive with or without disease after undergoing surgical resection of the LR and DM lesions. Because the follow-up period for patients with LR/DM (median 65 months, range 10–208 months) and those without LR/DM (median 32 months, range 2–273 months) were not significantly different ($P = 0.934$), these results suggested that surgical treatment of resectable LR or DM lesions could significantly improve the OS in a subset of LMSoB patients who develop LR or DM following the initial treatment.

With regard to the prognostic factors, patients who underwent definitive surgery or surgery with negative margins were proven to have significantly longer OS and DFS. This again emphasizes the importance of surgical treatment, and suggests that the clinical outcome of LMSoB is simply affected by whether an operation with a wide margin is possible or not. Moreover, the current chemotherapy regimens had little impact on the improvement of survival unlike other types of chemosensitive primary bone sarcoma, such as osteosarcoma in children and young adults [20].

Although the difficulty in diagnosing LMSoB has been discussed in past reports, our study has shown that the number of patients who are diagnosed with LMSoB has been increasing steadily over the past 20 years (Suppl Fig. S2). Furthermore, the histological diagnosis at biopsy showed fairly high accuracy (67.4%). This may be due to the increasing recognition of the existence of LMSoB and the usage of the immunohistological staining of smooth muscle specific markers such as SMA, desmin, HHF35, and h-caldesmon. Although the method for distinguishing LMSoB from MFH/pleomorphic sarcoma, spindle cell sarcoma, and fibrosarcoma [7] has to be further discussed, we found that osteosarcoma was excluded from the diagnosis in more than 90% LMSoB patients before surgical treatment. This fact will help in introducing neoadjuvant chemotherapy regimens other than those that are used to treat osteosarcoma before surgery.

The effects of chemotherapy in LMSoB have not been fully analyzed in the past. Fortunately, we were able to collect a significant number of patients who underwent neoadjuvant chemotherapy. Moreover, more than 80% of the first-line neoadjuvant chemotherapy regimens included cisplatin, meaning that most of neoadjuvant chemotherapy regimens were based on an osteosarcoma protocol. No patient who received a cisplatin-based chemotherapy protocol achieved a good response in both the radiological and histological evaluations. Furthermore, the 5-year metastasis-free survival rate of patients who received a cisplatin-based chemotherapy regimen was 39.8%, which did not differ to a statistically significant extent from the 5-year metastasis-free survival rate of patients who did not receive neoadjuvant chemotherapy (49.6%, $P = 0.512$). This indicates that cisplatin-based osteosarcoma protocols are not appropriate as neoadjuvant chemotherapy regimens for patients with LMSoB.

The efficacy of chemotherapy for LMS at primary sites other than the bone has been noted in the past reports. Ifosfamide-doxorubicin is the first-line protocol for soft tissue LMS; however, its efficacy is relatively low in comparison to other soft tissue sarcomas [21,22]. Vascular LMS is reported to have a limited response toward chemotherapy [23]. On the other hand, three regimens have been shown to improve progression-free survival in patients with uterine and soft tissue LMS, namely: gemcitabine plus docetaxel (uterine LMS), trabectedin plus doxorubicin (uterine and soft tissue LMS), and eribulin (soft tissue LMS) [12–15]. In the present study, one patient who received gemcitabine-docetaxel as a neoadjuvant chemotherapy achieved a PR in a radiological evaluation. Although the efficacy of gemcitabine-docetaxel as a neoadjuvant chemotherapy regimen in patients with LMSoB needs to be further evaluated, it could be a good candidate for a pathology-driven chemotherapy treatment in patients with LMSoB.

This study is associated with several limitations. Although this study is the largest LMSoB case series ever reported, the number of patients was relatively small due to its rarity. The retrospective nature of this study also has to be considered. The present study also lacked precise analysis concerning the dose and intensity of chemotherapy. To reveal the precise clinical outcomes and the chemosensitivity of LMSoB, a large multicenter prospective study of LMSoB patients who receive neoadjuvant chemotherapy is awaited.

CONCLUSIONS

Our study analyzed 48 LMSoB patients who were treated in Japan, which turned out to be the largest case series ever reported. The 5-year OS and DFS were 78.3% and 44.9%, respectively. The metastatic state at the first visit, the performance of definitive surgery and negative surgical margins were the prognostic factors for OS or DFS in a univariate analysis; while neoadjuvant chemotherapy regimens that include cisplatin, which accounts for the majority of neoadjuvant regimens in Japan, was associated with a poor response rate. This result suggests that surgical treatment with wide margins is the only treatment that was proven to be effective for LMSoB, and underscores the need to seek a novel chemotherapy regimen which is effective for LMSoB.

ACKNOWLEDGMENTS

The authors wish to express the deepest appreciation to all the members of JMOG for the information about the patients. Much information and support was provided by Dr. Takahiro Gotoh, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Dr. Ukei Anazawa, Tokyo Dental College Ichikawa General Hospital, Dr. Kayo Suzuki, Toyama University Hospital, Dr. Shunzi Nishimura, Kinki University Hospital, Dr. Keisuke Ae, The Cancer Institute Hospital of JFCR, Dr. Akihito Nagano, Gifu University Hospital, Dr. Yusuke Shinoda, The University of Tokyo Hospital, Dr. Takanori Wakayama, Saitama Medical University International Medical Center, Dr. Yoshiyuki Suehara, Jyuntendo University Hospital, Dr. Akihiko Matsumine, Mie University Hospital, Dr. Toshiyuki Kunisada, Okayama University Hospital, Dr. Yutaka Aoki, Kanazawa University Hospital, Dr. Toshiharu Shirai, Kyoto Prefectural University Hospital and Dr. Masato Sugawara, Yamagata University Hositipal.

REFERENCES

1. Abraham JA, Weaver MJ, Hornick JL, et al.: Outcomes and prognostic factors for a consecutive case series of 115 patients with somatic leiomyosarcoma. J Bone Joint Surg Am 2012;94:736–744.
2. Evans DM, Sanerkin NG: Primary leiomyosarcoma of bone. J Pathol Bacteriol 1965;90:348–350.
3. Adelani MA, Schultenover SJ, Holt GE, et al.: Primary leiomyosarcoma of extragnathic bone. Arch Pathol Lab Med 2009;133:1448–1456.
4. Antonescu CR, Erlandson RA, Huvos AG: Primary leiomyosarcoma of bone: A clinicopathologic, immunohistochemical, and ultrastructural study of 33 patients and a literature review. Am J Surg Pathol 1997;21:1281–1294.
5. Berlin O, Angervall L, Kindblom LG, et al.: Primary leiomyosarcoma of bone. Skeletal Radiol 1987;16:364–376.
6. Rekhi B, Kaur A, Puri A, et al.: Primary leiomyosarcoma of bone-a clinicopathologic study of 8 uncommon cases with immunohistochemical analysis and clinical outcomes. Ann Diagn Pathol 2011;15:147–156.
7. Ueda T, Araki N, Mano M, et al.: Frequent expression of smooth muscle markers in malignant fibrous histiocytoma of bone. J Clin Pathol 2002;55:853–858.
8. Angervall L, Berlin O, Kindblom LG, et al.: Primary leiomyosarcoma of bone: A study of five cases. Cancer 1980;46:1270–1279.
9. Myers JL, Arocho J, Bernreuter W, et al.: Leiomyosarcoma of bone: A clinicopathologic, immunohistochemical, and ultrastructural study of five cases. Cancer 1991;67:1051–1056.
10. Bouaziz MC, Chaabane S, Mrad K, et al.: Primary leiomyosarcoma of bone: Report of 4 cases. J Comput Assist Tomogr 2005;29:254–259.
11. Brewer P, Sumathi V, Grimer RJ, et al.: Primary leiomyosarcoma of bone: Analysis of prognosis. Sarcoma 2012;2012:636849.
12. Hensley ML, Ishill N, Soslow R, et al.: Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: Results of a prospective study. Gynecol Oncol 2009;112:563–567.
13. Monk BJ, Blessing JA, Street DG, et al.: A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: A gynecologic oncology group study. Gynecol Oncol 2012;124:48–52.
14. Pautier P, Floquet A, Chevreau C, et al.: Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): A non-randomised, multicentre, phase 2 trial. Lancet 2015;16:457–464.
15. Schöffski P, Ray-Coquard IL, Cioffi A, et al.: Activity of eribulin mesylate in patients with soft-tissue sarcoma: A phase 2 study in four independent histological subtypes. Lancet Oncol 2011;12:1045–1052.
16. Edge SB, Compton CC: The American joint committee on cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–1474.
17. Enneking WF: A system of staging musculoskelneoplasms. Clin Orthop Relat Res 1986;204:9–24.
18. Eisenhauer EA, Therasse P, Bogaerts J, et al.: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.
19. Huvos AG, Rosen G, Marcove RC: Primary osteogenic sarcoma: Pathologic aspects in 20 patients after treatment with chemotherapy en bloc resection, and prosthetic bone replacement. Arch Pathol Lab Med 1977;101:14–18.
20. Anninga JK, Gelderblom H, Fiocco M, et al.: Chemotherapeutic adjuvant therapy for osteosarcoma: Where do we stand? Eur J Cancer 2011;47:2431–2445.
21. Scurr M: Histology-driven chemotherapy in soft tissue sarcoma. Curr Treat Options Oncol 2011;12:32–45.
22. Clark MA, Fisher C, Judson I, et al.: Soft-tissue sarcoma in adults. N Engl J Med 2005;353:701–711.
23. Gage MJ, Patel AV, Koenig KL, et al.: Non-vena cava venous leiomyosarcomas: A review of the literature. Ann Surg Oncol 2012;19:3368–3374.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.