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ORIGINAL ARTICLE

Current Status of Uterine Leiomyosarcoma in the Tohoku Region: Results of the Tohoku Translational Center Development Network Survey

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Abstract

Background To prepare for a future clinical trial for improving the long-term prognosis of patients with uterine leiomyosarcoma (ULMS), we conducted a multi-institutional survey in the Tohoku region of Japan.

Methods We conducted a retrospective cohort study between 2011 and 2014 in member institutions of the Tohoku Translational Research Center Development Network.

Results A total of 53 patients with ULMS were registered in 31 institutions for the present survey. The median patient age was 56 years, 67.9% of the patients were postmenopausal, 88.7% had a performance status of 0 or 1, and only 6 patients (11.3%) showed preoperative evidence of malignancy. Although retroperitoneal lymphadenectomy was performed in only 26.4% of patients, 64.2% patients were identified as having FIGO stage 1 disease; 73.6% were eligible to undergo complete surgery. Among 36 patients who were treated with postoperative chemotherapy, 28 (77.8%)

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received docetaxel and gemcitabine combination therapy. The most frequent recurrence site was the lungs, and the median progression-free survival of all enrolled patients was 11.7 months. However, the median progression-free survival and the median overall survival in patients with stages III and IV disease were 3.4 and 11.4 months, respectively.

Conclusion Although ULMS was associated with a high rate of complete or optimal surgery, the long-term prognosis was poor. Effective postoperative therapy should be developed to improve the long-term prognosis of patients with ULMS.

Keywords Uterine leiomyosarcoma · Tohoku region · Retrospective survey

Introduction

Uterine leiomyosarcoma (ULMS) is a rare malignancy with a poor prognosis. There were 1213 ULMS cases (0.55 per 1,00,000) in Caucasian women and 234 cases (0.92 per 1,00,000) in African–American women reported between 1978 and 2001 in 9 areas of the Surveillance, Epidemiology, and End Results (SEER) program [1]. A Norwegian survey also reported that 476 cases, 1.7 per 1,00,000 women [2], were registered between 1956 and 1992, and a separate study reported that 259 cases were registered between 1970 and 2000 [3]. Furthermore, 208 cases were reported at the Mayo Clinic between 1976 and 1999 [4]. In Japan, 40 cases were reported between 1990 and 1999 by 14 institutions in Hokkaido [5], 36 cases between 1990 and 2003 by 13 institutions in the Kinki distinct [6], and 31 cases between 1990 and 2004 by 17 institutions in the Tohoku region [7]. However, because ULMS surgery has been often performed at general hospitals under the preoperative diagnosis of benign uterine myoma, it is difficult to confirm the actual number of ULMS cases.

Tohoku Translational Research Center Network (TTN) was constructed as a part of the Project of Translational and Clinical Research Core Centers by the Japanese Ministry of Health, Labour and Welfare for development of clinical trials, clinical research, and the innovation of clinical devices as an academic research organization comprising 6 universities and affiliate hospitals in the Tohoku region. We conducted a retrospective survey across the TTN participant institutions to better understand ULMS and construct a patient registry for conducting future clinical trials to improve the long-term prognosis of patients with ULMS.

Patients and methods

We investigated the clinical conditions of patients who were treated between January 2011 and December 2014. The clinical data were treated year, name of prefecture, name of institution, patient's age, performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG), menstruation status, preoperative diagnosis, preoperative evidence of malignancy, date of initial surgery, completion of initial surgery, existence of retroperitoneal lymphadenectomy, retroperitoneal lymph node metastasis, stage according to the International Federation of Obstetrics and Gynecology (FIGO, 2008), postoperative chemotherapy regimen, recurrence sites, date of recurrence, date of last follow-up, and prognosis. Overall survival (OS) was defined as the time between the initial treatment and death from any cause, and progression-free survival (PFS) was defined as the time between the initial treatment and the first evidence of disease progression or death from any cause. The Kaplan–Meier method was used to calculate OS and PFS curves. All data analyses were performed using R software, version 3.2.1. (R Foundation for Statistical Computing, Vienna, Austria). The present survey was approved by the ethics committee of Tohoku University Graduate School of Medicine and each of the participating institutions.

Results

A total of 53 ULMS patients were registered from the following 31 institutions: Akita City Hospital; Akita University Graduate School of Medicine and Faculty of Medicine; Aomori Kousei Hospital; Fukushima Medical University; Hachinohe City Hospital; Hirosaki National Hospital; Hirosaki University Graduate School of Medicine; Iwaki Kyoritu Hospital; Iwate Medical University; Iwate Prefectural

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Central Hospital; Iwate Prefectural Chubu Hospital; Iwate Prefectural Iwai Hospital; Japanese Red Cross Akita Hospital; Japanese Red Cross Ishinomaki Hospital; Kesennuma City Hospital; KKR Tohoku Kosai Hospital; Miyagi Cancer Center; Nakadori General Hospital; Nihonkai General Hospital; Noshiro Kousei Medical Center; Ohta Nishinouchi Hospital; Omagari Kousei Medical Center; Osaki Citizen Hospital; Saka General Hospital; Sendai City Hospital; Sendai Medical Center; Takeda General Hospital; Tohoku University Graduate School of Medicine; Yamagata Saisei Hospital; Yamagata Prefectural Central Hospital; and Yamagata University Faculty of Medicine.

The median patient age was 56 years, 67.9% of them were menopausal, and 88.7% had a PS of 0 or 1. Thirteen (24.5%) patients were preoperatively diagnosed with benign uterine myoma, and only 6 (11.3%) patients had preoperative confirmation of malignancy, based on histological or cytological evidence. Furthermore, 75.5% underwent complete or optimal (maximum diameter of residual tumor ≤1 cm) surgery (Table 1). Although 39 patients (73.6%) did not undergo retroperitoneal

Table 1 Patient characteristics

Total number of patients registered	53
Treatment year	
2011	13
2012	16
2013	12
2014	12
Median age (range)	56 years (34–82)
Menstrual status	
Pre-menopause	17
Menopause	36
ECOG performance status	
0	24
1	23
2	4
3	1
4	1
Preoperative diagnosis	
Myoma	13
Suspected sarcoma	32
Sarcoma	6
By cytology	2
By histology	4
Ovarian tumor	2
Surgery	
Complete	39
Optimal	1
Suboptimal	9
Biopsy	3
Not performed	1
Retroperitoneal lymph nodes dissection	
Performed	14
Not performed	39

ECOG Eastern Cooperative Oncology Group

Optimal surgery: maximum diameter of residual tumor ≤1 cm

Table 2 Clinicopathological features of patients

Retroperitoneal lymph node metastasis	
Positive	2
Negative	12
Unknown	39
FIGO (2008) stage	3
1A[a]	3
B[b]	31
2A	1
B[c]	5
3A[d]	4
B	1
C	2
4[e]	6
Chemotherapy regimens	
DG	28
IAP	2
CAP	1
AI	1
Anthracycline alone	4
Not performed	16
Unknown	1
Recurrence site[f] (in patients receiving complete surgery)	
Lungs	9
Intra-pelvic	5
Intra-abdominal	2
Liver	1
Bone	3
Subcutaneous tissue	1
Prognosis	
Alive and disease-free	25
Alive with disease	9
Died of disease progression	19

FIGO International Federation of Obstetrics and Gynecology, *DG* docetaxel and gemcitabine, *IAP* ifosfamide, adriamycin, and cisplatin, *CAP* cyclophosphamide, adriamycin, and cisplatin, *AI* ifosfamide and adriamycin, anthracycline, adriamycin or epirubicin

[a] 2 patients did not receive retroperitoneal lymphadenectomy

[b] 24 patients did not receive retroperitoneal lymphadenectomy

[c] All patients did not receive retroperitoneal lymphadenectomy

[d] 3 patients did not receive retroperitoneal lymphadenectomy

[e] 5 patients did not receive retroperitoneal lymphadenectomy

[f] Multiple recurrence sites were counted

lymphadenectomy, 2 patients were diagnosed with retroperitoneal lymph node metastasis. Most patients had FIGO stage 1 disease (64.2%). Thirty-six (67.9%) patients received postoperative chemotherapy, and 28 were treated with a combination of docetaxel and gemcitabine. The most frequent recurrence site in the 39 patients who underwent complete surgery was the lungs ($n = 9$), and 19 patients died of disease progression (Table 2). The median PFS of all registered patients was 11.7 months (Fig. 1) and median OS was not reached (Fig. 2). However, the median PFS and median OS for FIGO stage III/IV disease were 3.4 months (Fig. 3) and 11.4 months (Fig. 4), respectively. The survival results of the present study in patients with ULMS are very similar to those of previous studies (Table 3).

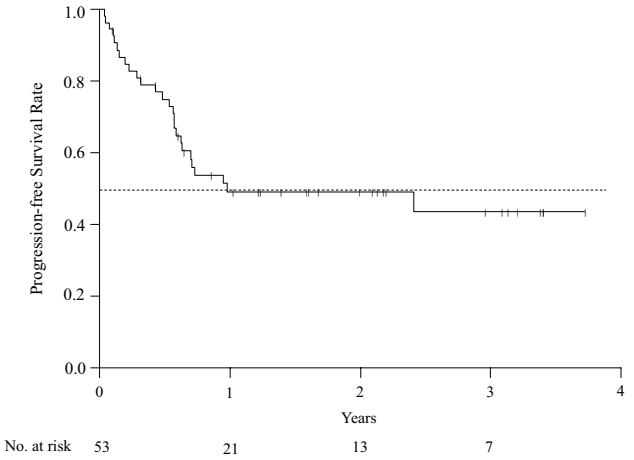

Fig. 1 Progression-free survival of all enrolled patients. The median progression-free survival was 11.7 months

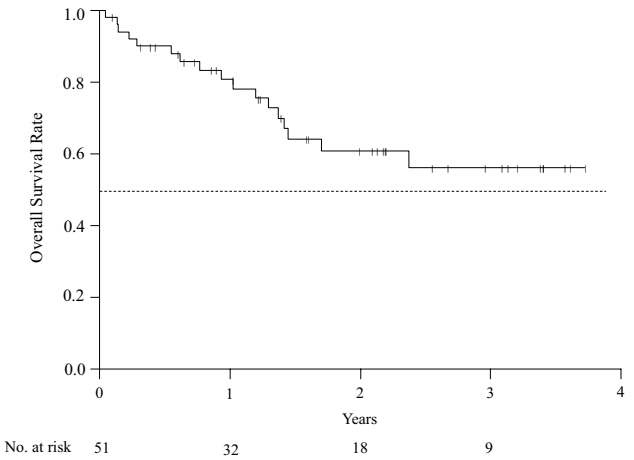

Fig. 2 Progression-free survival according to FIGO stage. The progression-free survival of patients with stage I–II disease was not reached. The progression-free survival of patients with stages III–IV disease was 3.4 months

Discussion

A previous survey reported that the annual caseload of ULMS for university hospitals and special hospitals in the Tohoku region is only 3–4 cases [7]. However, the present survey, which included general hospitals, revealed that almost 12 cases were treated in a year in the Tohoku region. Only 11% of our patients showed preoperative cytological or pathological evidence of malignancy. The other patients with ULMS received surgical treatment based on preoperative diagnoses of benign leiomyoma and suspected sarcoma. Therefore, many ULMS patients have been treated at general hospitals, unlike those with cervical cancer, endometrial cancer, or ovarian

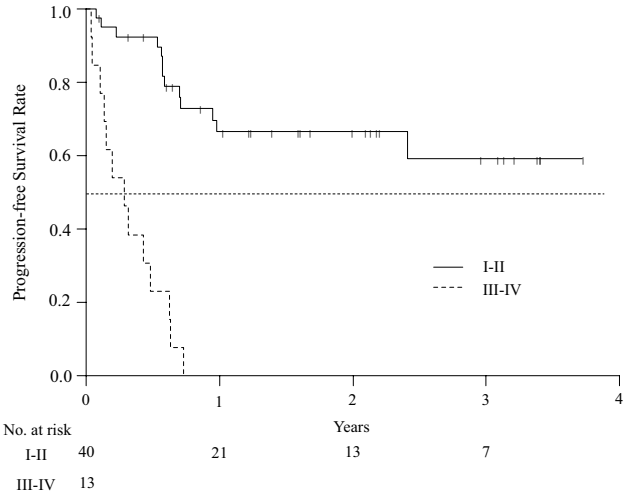

Fig. 3 Overall survival of all enrolled patients. The median overall survival was not reached

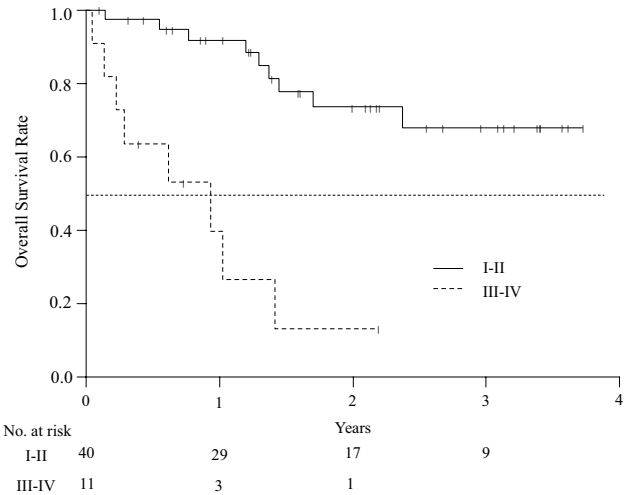

Fig. 4 Overall survival according to FIGO stage. The overall survival of patients with stage I–II disease was not reached. The overall survival of patients with stages III–IV disease was 11.4 months

Table 3 Results of previous studies

Author	Total number of cases	Study period (Total)	FIGO stage	(%)	Prognosis
Gadducci [8]	126	1980–1994 (15 years)	I	69.8	Median time to recurrence: 11 months
			II	1.6	
			III	12.7	
			IV	15.9	
Mayerhofer [9]	71	1973–1995 (23 years)	I	69	Median disease-free survival: 8 months
			II	7	
			III	10	
			IV	14	
Giuntoli II [10]	208	1976–1999 (24 years)	I	62	Median disease specific survival: 4.9 years
			II	6	
			III	9	
			IV	20	
Sagae [5]	106	1990–1999 (10 years)	I	75	5-year disease-free survival Stage I: 54.5 and Stage II: 100%
			II	3	Stages III and IV: 0%
			III	12	5-year overall survival rate Stage I: 73.0 and Stage II: 100%
			IV	10	Stages III and IV: 0%
Kokawa [6]	36	1990–2003 (14 years)	I	41.7	1-year survival rate: 57.6%
			II	8.3	2-year survival rate: 41.4%
			III	22.2	5-year survival rate: 16.0%
			IV	27.8	
Akahira [7]	31	1990–2004 (15 years)	I	54.8	Median overall survival Stages I and II: not reached
			II	3.2	Stages III and IV: 400 days
			III	25.8	5-year overall survival rate: 61.3%
			IV	16.2	
Abeler [3]	223[b]	1970–2000 (31 years)	I	80	5-year overall survival rate Stage I: 51 and stage II: 25%
			II	14	Stages III and IV: 0%
			III	6	
			IV	0	
Farid [11]	51	2002–2010 (9 years)	Nonmetastatic	70.6	Median overall survival: 49.8 months
			Metastatic	29.4	Median disease-free survival of patients with nonmetastatic disease: 31.3 months
Rauh-Hain [12]	167	2000–2010 (11 years)	I	55	Median overall survival Stage I: 75 months Stage II: 66 months
			II	4	Stage III: 34 months Stage IV: 20 months
			III	11	
			IV	30	
Garcia [13]	75	1999–2007 (9 years)	I	65.4	Overall survival rate Stage I: 64% (3 years), 38% (5 years)
			II	2.6	Stage II–IV: 30% (3 and 5 years)
			III	5.3	
			IV	26.7	
Present study	53	2011–2014 (4 years)	I	64.2	Median progression-free survival: 11.7 months
			II	11.3	Median overall survival: not reached
			III	13.2	
			IV	11.3	

cancer. Furthermore, although patients with ULMS had good PS and a high rate of complete or optimal surgery, the long-term prognosis remains poor [8–13]. Although previous studies [4, 8, 13, 14] have revealed that adjuvant therapy was not associated with a significant survival benefit even in early stage ULMS, the effects of a new

combination chemotherapy or molecular-targeted therapy have been evaluated in clinical trials to improve the prognosis of patients with ULMS. Combination therapy of gemcitabine and docetaxel has been a standard regimen of chemotherapy according to results of phase II trials [15–17], and there have been favorable results from a phase II trial (SARC 005) regarding adjuvant treatment with docetaxel and gemcitabine followed by doxorubicin in patients with uterus-limited ULMS [18]. However, our previous report revealed that dose reduction due to bone marrow suppression was frequently required with docetaxel and gemcitabine therapy, especially in Japanese patients [19]. According to the results of previous studies, clinical features of ULMS were although FIGO stage was distributed early stage, but exhibited a poor prognosis (Table 3). Therefore, the development of more effective and acceptable regimen for ULMS is an urgent issue. Recently, a phase III trial by the European Organization of Research and Treatment of Cancer reported that a multikinase angiogenesis inhibitor, pazopanib, exhibited superior results in PFS compared with a placebo in patients with advanced non-adipocytic soft tissue sarcoma [20]. Furthermore, trabectedin and eribulin were approved as agents for the treatment of malignant soft tissue sarcoma in Japan in 2015 and 2016, respectively, following the results of phase III studies comparing them with dacarbazine [21, 22]. More recently, olaratumab, a human antiplatelet-derived growth factor receptor α monoclonal antibody, when administered with doxorubicin, improved the outcomes of patients with unresectable or metastatic soft-tissue sarcoma compared to doxorubicin alone [23]. Although olaratumab is not approved in Japan, this agent can be expected to have a treatment effect for ULMS.

Because the present study clearly demonstrates that patients with ULMS show good PS and a high rate of complete or optimal surgery, a new clinical trial of adjuvant therapy to improve the long-term prognosis of patients with ULMS is warranted. However, accurate pathological diagnosis is an important factor for ULMS. Therefore, we established a TTN central pathological review board for conducting an upcoming clinical trial in Japan.

Compliance with ethical standards

Conflict of interest Authors have no conflict of interest to declare.

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