Clinical research

Uterine sarcomas: clinical characteristics, management, and outcomes – a single centre's experience

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Abstract

Introduction: The purpose of the present study is to evaluate the clinical presentation, histopathologic pattern and outcome of uterine sarcomas in a single institution of gynaecological oncology.
Material and methods: The database of the Gynecologic Oncology Department of the hospital was used to identify patients diagnosed with pathological uterine sarcoma treated between January 1, 2004, and December 31, 2015. We collected clinicopathological data to evaluate factors that are important for overall survival (OS).
Results: A total of 54 cases were included in the analysis: 25 uterine leiomyosarcomas (LMS), 19 carcinosarcomas (CS) and nine endometrial stromal sarcomas (ESS). The mean age was 53.8 years for LMS, 62.1 years for CS. Disease recurrence occurred in 13 (24.0%) patients. The recurrent disease occurred in the pelvis in nine patients, but it was characterised by distant metastases (liver or mediastinal lymph nodes) in the other four patients Having had a lymphadenectomy and adjuvant chemotherapy for CS and advanced stage for LMS were the only factors for which a significant difference in OS was observed ($p = 0.035$, $p = 0.006$ and $p = 0.04$, respectively). In contrast, for CS, only not having adjuvant chemotherapy showed a significant association with poor disease free survival.
Conclusions: Lymphadenectomy and adjuvant chemotherapy had a significant impact on OS for CS, and advanced stage was the only independent predictor of OS for LMS.

Key words: uterine sarcoma, lymphadenectomy, advanced stage, adjuvant chemotherapy

Introduction

Uterine sarcomas are highly malignant tumours that account for 2–5% of all uterine malignancies and < 1% of gynaecological malignancies [1]. These tumours usually have aggressive clinical behaviour, and

local recurrence and distant metastases are frequent [2]. Because of the rarity and histopathological diversity of uterine sarcomas, there is a lack of consensus on the risk factors, poor outcome and optimal treatment strategy [1]. Overall survival is poor, with 5-year survival rates of 50–70% for stage 1 disease and, dramatically, 0–20% for the remaining stages. Histologically, uterine sarcomas are classified into three main pathological subgroups: carcinosarcomas (CS) (40%), leiomyosarcomas (LMS) (40%) and endometrial stromal sarcomas (ESS) (10–15%) [3–5].

The prognostic factors usually reported include tumour stage, histological subtype, grade, lymphovascular invasion, menopausal status and adjuvant radiotherapy. The strongest prognostic factor for all subgroups is the stage at diagnosis [5–7]. Different staging systems exist for ESS and LMS, while CS follows that of endometrial carcinoma. Stage I LMS and ESS are classified according to tumour size, while the subdivision of stage I adenosarcomas (AS) considers myometrial invasion [8]. Abdominal or pelvic mass, pain and abnormal uterine bleeding are the most frequently reported symptoms for all subgroups. The management of sarcomas has been controversial. Surgery is the primary treatment for sarcomas; however, due to their rarity, surgical management has not been well defined. The necessity of lymph node dissection varies by tumour histology. Women with LMS or undifferentiated endometrial sarcoma are not eligible for routine systematic pelvic and paraaortic lymphadenectomy. The role of lymphadenectomy in ESS is unknown and selective pelvic and paraaortic node dissection may be reasonable [9]. In addition, the high rates of both local and distant recurrence after surgery suggest a need for effective adjuvant therapies, although the benefits of adjuvant chemotherapy, radiotherapy and hormonal therapy are unclear [10].

The aim of the present study is to evaluate the clinical presentation, histopathologic patterns and outcome of uterine sarcomas in our hospital.

Material and methods

The database of the Gynecologic Oncology Department at our hospital was used to identify patients diagnosed with pathological uterine sarcoma who were treated between January 1, 2004, and December 31, 2015. This study was conducted by the ethical standards of the Declaration of Helsinki and was approved by the local ethics committee.

The following clinical data were collected from patient medical, surgical and pathological reports: demographic characteristics, presenting symptoms, serum cancer antigen 125 (CA-125) level, date and type of surgical procedure, number of excised and positive lymph nodes, pathological tumour characteristics (grade and size), histological type, adjuvant therapy (if any), date of recurrence, treatment after recurrence, date of last medical examination and date of death. The International Federation of Gynecology and Obstetrics (FIGO) 2009 staging for uterine sarcomas was used for all patients. Staging groups were classified as early FIGO stage (I–II) and advanced stage (III–IV). All operations were performed by laparotomy.

Adjuvant radiation therapy (RT) or chemotherapy (CT) was planned by the members of the tumour board, depending on the clinical and pathological characteristics discovered during surgical staging. External beam radiotherapy (EBRT) was administered at a median dose of 50.4 Gy (range: 45–54 Gy) at 1.8–2.0 Gy per fraction, 5 days per week. Vaginal vault brachytherapy (VBT) (2 × 650 cGy, prescribed to 0.5-cm depth) was delivered using a vaginal applicator with a high-dose-rate iridium-192 source.

The patients were examined every three months for the first 2 years, every 6 months for the following 3 years, and annually after that. Computed tomography or magnetic resonance imaging was performed annually. Analysis of survival data was conducted in December 2015.

Statistical analysis

The survival analysis was based on the Kaplan-Meier method, and the results were compared using a log-rank test. Disease-free survival (DFS) was determined as the time interval between the date of primary surgery and the detection of the first recurrence or the latest observation. Overall survival (OS) was defined as the time from the date of primary surgery to death or the latest observation. The χ^2 tests and Student's *t*-tests for unpaired data were used for statistical analysis. To determine the factors affecting survival, we used Cox regression analysis, which was presented as hazard ratios (HR). All statistical analyses were completed using MedCalc software (ver. 11.5 for Windows, MedCalc Software, Mariakerke, Belgium). A p-value < 0.05 was considered to indicate statistical significance.

Results

A total of 54 case records were retrieved for this retrospective analysis. Nine patients had ESS, 19 had CS, 25 patients had LMS, and one had AS. Patient characteristics are shown in Table I. The mean age of the patients was 53.8 ±1.6 years for LMS and 62.1 ±14.9 for CS. Most patients had a stage I disease. In all subtypes, the most common presenting complaint was abnormal vaginal bleeding. Other complaints included pain and

Table I. Patient characteristics

Parameter	ESS (%)	LMS (%)	CS (%)	AS (%)
Number of patients	9 (16.7)	25 (46.3)	19 (35.2)	1 (1.9)
Age	49.4 ±19.0	53.8 ±1.6	62.1 ±14.9	54.0 ±0.0
Parity	3.4 ±3.1	3.9 ±2.6	5.3 ±3.7	0
DM	2 (22.2)	3 (12)	5 (26.3)	0
Hypertension	3 (33.3)	3 (12)	11 (57.9)	0
Complaint:				
Bleeding	6 (66.7)	16 (64)	14 (73.7)	1 (100)
Pain	2 (22.2)	8 (32)	5 (26.3)	0
Mass effect	1 (11.1)	1 (4)	0	0
Tm size	6.4 ±5.4	8.8 ±5.0	6.3 ±4.9	4
Grade:				
I	5 (55.5)	13 (52)	4 (21.1)	0
II	2 (22.2)	6 (24)	1 (5.3)	0
III	2 (22.2)	6 (24)	14 (73.7)	1
Stage:				
Ia	3 (33.3)	8 (32)	5 (26.3)	0
Ib	4 (44.4)	10 (40)	3 (15.8)	1 (100)
IIa	0	0	0	0
IIb	0	5 (20)	0	0
IIIa	1 (11.1)	1 (4)	1 (5.3)	0
IIIb	0	0	3 (15.8)	0
IIIc	0	1 (4)	5 (26.3)	0
IVa	1 (11.1)	0	1 (5.3)	0
IVb	0	0	1 (5.3)	0
Preop CA 125	18.0 ±12.7	18.8 ±6.5	25.7 ±25.6	10.0
Recurrence	1 (11.1)	6 (24)	5 (26.3)	1 (100)
DFS	54.1 ±54.0	40.0 ±32.1	18.6 ±25.5	9.0 ±0.0
OS	54.6 ±53.5	43.0 ±30.2	20.1 ±25.1	24.0 ±0
Death	3 (33.3)	9 (36)	6 (31.5)	0

ESS – endometrial stromal sarcoma, CS – carcinosarcoma, LMS – leiomyosarcoma, AS – adenosarcoma, DFS – disease-free survival, OS – overall survival.

mass effects. The mean follow-up period was 36 months (range: 2–132 months). During this period, 18 patients died. The percentage of patients with hypertension was higher in the CS group (57.9%). The patient characteristics are shown in Table I.

Treatment details are shown in Table II. All patients underwent surgery (with or without adjuvant treatment). For ESS and CS, the most common surgical procedures were the total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), washing cytology, pelvic-paraaortic lymph node dissection and omentectomy. For LMS, the most common surgery types were TAH and BSO. Twenty patients received chemoradiotherapy (CRT). Seven patients received only CT, and the most common regimens were cisplatin plus doxorubicin and cisplatin plus ifosfamide. Postoperative RT alone consisted of EBRT (n = 5/15 patients) and EBRT + VBT (n = 10/15 patients).

Recurrence management is shown in Table III. Disease recurrence occurred in 13 (24.0%) patients. The recurrent disease occurred in the pelvis in 9 patients, but it was characterised by distant metastases (liver or mediastinal lymph nodes) in the other 4 patients. Three patients were managed with secondary debulking surgery, 4 patients received CT, and 6 patients were managed with chemoradiotherapy (Table III).

The results of multivariate analyses of OS and DFS with LMS and CS are shown in Table IV. Having had a lymphadenectomy and adjuvant chemotherapy for CS and advanced stage for LMS were the only factors in which a significant difference in OS was observed (p = 0.035, p = 0.006 and p = 0.04, respectively). In contrast, for CS, only not having adjuvant chemotherapy showed a significant association with the poor DFS (Table IV).

Discussion

In the present study, we performed a retrospective analysis of data from 54 patients with sarcoma of the uterus who were treated in our gynaecological oncology centre in Turkey. We aimed to describe the demographic, clinical and surgical characteristics of uterine sarcoma and to identify the variables affecting OS and DFS in patients with this disease.

Most previous studies of uterine sarcomas have reported an incidence of 55% for LMS, this being the commonest; CS comes in second at 30%, while ESS is least common (15%) [2, 3]. In our study, LMS (46.3%) was the most frequent type, followed by CS (35.2%) and then ESS (16.7%), in line with the literature. In all subgroups, the most common presenting symptom was abnormal vaginal bleeding. The median age at diagnosis was 62 years for CS,

Table II. Surgical characteristics

Parameter	ESS (9)	LMS (25)	CS (19)	AS (1)
Surgical procedure:				
TAH + BSO + washing cytology + PPLND + omentectomy	5 (55.5)	3 (12.0)	11 (57.9)	0
TAH + BSO + washing cytology + PLND + omentectomy	2 (22.2)	8 (32)	8 (42.1)	0
TAH + BSO + washing cytology + PLND	1 (11.1)	2 (8)	0	1 (100)
TAH + BSO	1 (11.1)	12 (48.0)	0	0
Operation complication:				
Bleeding	2 (22.2)	0	6 (31.6)	0
Ureter injury	0	1 (4.0)	0	0
Bladder injury	0	2 (8.0)	0	0
Lymph node count:				
Pelvic	19.4 ±8.2	17.3 ±8.2	20.4 ±7.3	10.0
Paraaortic	9.0 ±5.0	11.9 ±11.6	13.4 ±9.2	0
Adjuvant treatment:				
CT	0	3 (12)	3 (15.7)	1 (100)
RT	2 (22.2)	6 (24)	7 (36.8)	0
HT	2 (22.2)	0	0	0
CRT	4 (44.4)	8 (32)	8 (42.1)	0

TAH – total abdominal hysterectomy, BSO – bilateral salpingoophorectomy, PPLND – pelvic and paraaortic lymphadenectomy, CT – chemotherapy, RT – radiation therapy, HT – hormonal therapy, CRT – chemoradiotherapy.

Table III. Recurrence management

Variable	ESS (1)	LMS (6)	CS (5)	AS (1)
Surgery	0	2 (33.3)	1 (20)	0
CT	0	4 (66.6)	0	0
CRT	1 (100)	0	4 (80)	1 (100)

CT – chemotherapy, CRT – chemoradiotherapy.

Table IV. Results of multivariate analysis of OS and DFS with LMS and CS

Parameter	CS (19)			LMS (25)		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
OS:						
Stage (III and IV vs. I and II)	1.2	0.6–2.3	0.41	4.6	2.6–8.9	0.04
Lymphadenectomy	0.5	0.2–1.2	0.035	0.8	0.6–1.1	0.20
Adjuvant chemotherapy	0.2	0.1–0.4	0.006	0.9	0.4–1.7	0.16
DFS:						
Stage (III and IV vs. I and II)	1.3	0.5–3.1	0.72	2.1	1.2–4.0	0.06
Lymphadenectomy	0.7	0.4–1.3	0.09	0.9	0.6–1.4	0.16
Adjuvant chemotherapy	0.2	0.1–0.4	0.009	0.8	0.4–1.6	0.36

53 years for LMS and 49 years for ESS, figures in accordance with the previous literature [11]. In a previous study, the surgical stage was found to be the most important prognostic indicator for CS and LMS [10]. However, we found that advanced stage was a significant prognostic factor for LMS, but not for CS. This contrast in results may be attributable to the small number of CS patients in our study.

Currently, no guidelines have been established for the management of uterine carcinosarcoma. Though surgery is the cornerstone of the treatment, the extent to which surgical procedures can benefit patients remains unknown. TAH and BSO are the most common procedures; the additive benefit of systematic lymphadenectomy remains undetermined, especially for LMS and ESS patients [12]. Vorgias and Fotiou recommended performing lymphadenectomy in patients with CS [13]. Nemani *et al.* reported a significant OS benefit associated with lymphadenectomy, with a 5-year OS of 49%, compared with 35% for patients who had not undergone lymphadenectomy [14]. In the present study, we found that CS patients receiving lymphadenectomy had significantly higher OS, in line with the literature. The gold standard of management for LMS is surgery, and patients with suspected or confirmed LMS should have their uterus removed en bloc, with maximal effort to avoid intraoperative rupture or spillage of the tumour into the peritoneal cavity [15]. The incidence of retroperitoneal lymph node metastases is low for LMS; therefore, pelvic and paraaortic lymph node dissection is not recommended in routine practice, even for patients who have been found to have lymph node involvement [16]. Like other researchers, we also found that having a lymphadenectomy had no significant impact on OS in LMS patients.

There is still a controversy surrounding the most suitable method for adjuvant treatment of CS. Menczer *et al.* reported a multicentre study comparing CT with or without radiation to RT alone in patients who underwent surgical staging for CS. The authors reported that sequential treatment after surgery reduced mortality when compared to patients taking RT or CT alone [17]. In our study, we found that surgery followed by CT gave a significantly longer median OS and DFS for early- and advanced-stage CS. The benefits of CT as an adjuvant treatment for LMS patients who had complete resection for the uterus-limited disease are also controversial. In a multicentric retrospective study that evaluated the role of adjuvant treatment for 140 women with stage I/II LMS after surgery, the results showed that adjuvant CT was not associated with a significant survival benefit (68.7% in the CT vs. 65.6% in the observation group, $p = 0.521$) [18]. This finding was similar to ours.

The ESS was divided into the endometrial stromal nodule, low-grade endometrial stromal sarcoma (LG-ESS) and undifferentiated endometrial sarcoma [2]. The endometrial stromal nodule's prognosis is good, and a hysterectomy was adequate for the treatment. The LG-ESS is an indolent tumour with a favourable prognosis, but it is characterised by delayed recurrences even in patients with an early stage disease, suggesting the need for long-term follow-up [19]. A review of the literature shows that recurrent LG-ESS can occur 10–20 years after the initial diagnosis [20]. Undifferentiated endometrial sarcomas have a poor prognosis, and most patients die of the disease within 2 years of diagnosis [21]. Because there were only 9 cases of ESS, we did not perform survival analysis in this subgroup.

This study has several limitations. First, it was a retrospective analysis. Second, there were only 54 patients evaluated. Despite these limitations, the fact that this study evaluated a single centre database and used data from a long follow-up period increases the validity of its results and limits its weaknesses.

In conclusion, the two most important findings of our study are that: 1) lymphadenectomy and adjuvant chemotherapy had a significant impact on OS for CS, and 2) advanced stage was the only independent predictor of OS for LMS. A multicentre randomised clinical trial that includes a large number of patients is needed to determine the optimal management of this disease definitively.

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Conflict of interest

The authors declare no conflict of interest.

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