Prognostic factors and survival outcomes of uterine sarcomas in a reference gynecologic oncology cancer center

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Ethics Committee Approval
The study protocol was approved by the Tepecik Education and Research Hospital Ethics Committee with the number 2021/01-47 on 15/01/2021.

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 March 19

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How to cite: Demirtaş GS, Gökçü M. Prognostic factors and survival outcomes of uterine sarcomas in a reference gynecologic oncology cancer center. J Surg Med. 2021;5(3):215-220.

Abstract

Background/Aim: Uterine sarcomas are rare and aggressive tumors, and their clinical behavior is unpredictable. A clear-cut clinical course, proven treatment method or definitive prognostic factors affecting the survival of sarcoma patients are not reported in the literature. We aim to evaluate uterine sarcomas, determine clinicopathologic features, adjuvant therapies, and prognostic factors on survival while sharing our experience of these rare uterine tumors in light of the literature.

Methods: This retrospective cohort study was conducted in Tepecik Training and Research Hospital, Izmir, Turkey between 2002-2020. Out of the total of 205 uterine sarcoma patients, 173 patients who underwent surgical procedures and were followed up in our hospital’s Gynecologic Oncology Clinic were included in the study. Data of patients were collected from the hospital database. Surgical interventions, clinicopathologic features, adjuvant therapies, and overall and disease-free survivals were evaluated. Patients were grouped as leiomyosarcoma (LMS), carcinosarcoma (CS), endometrial stromal sarcoma (ESS), adenosarcoma (AS), and undifferentiated sarcoma (US).

Results: The mean age of the patients was 57.6 (11.2) years. According to the International Federation of Gynecology and Obstetrics (FIGO2009), 115 patients (66.5%) had stage 1, 17 patients (9.8%) had stage 2, 31 (17.9%) patients had stage 3, and 10 patients (5.8%) had stage 4 disease. One hundred and sixty-two patients (93.6%) received adjuvant therapy. Median follow-up period was 39 months (range 3-214). The 120-month OS for the entire group was 87.1%.

Conclusion: Stage is a significant prognostic factor for survival in all sarcoma types and recurrence is a significant prognostic factor for survival for LMS and CS patients. Sarcoma type and adjuvant treatments have no impact on survival. ESS patients require extended surgical staging.

Keywords: Uterine sarcoma, Chemotherapy, Radiotherapy, Survival
Introduction

Uterine sarcomas are rare and aggressive tumors of the uterus which account for up to 7% of all uterine cancers [1]. In 1959, Ober classified these tumors according to their origin and cell types. In 2009, a new FIGO classification and staging system was published [2]. Histological sarcoma types include malignant mixed Mullerian tumors (MMMT, or carcinosarcomas (CS)), leiomyosarcomas (LMS), endometrial stromal sarcomas (ESS) and undifferentiated sarcomas (US). Carcinosarcomas are still staged as uterine carcinomas. In all uterine sarcomas, the most common presenting symptoms are abnormal uterine bleeding and pelvic mass. Stage is the most important prognostic factor for uterine sarcomas [3]. Since uterine sarcomas are rare, risk factors and a definitive treatment protocol have not been established. In terms of adjuvant treatments, postoperative radiation therapy seems to improve local control [4].

The purpose of this study was to compare histological subtypes and clinical outcomes with analysis of the role of adjuvant therapies in the management of these patients and share our experience of management of these rare tumors in light of the literature.

Materials and methods

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Tepeck Training and Research Hospital Ethics Committee with the number 2021/01-47 on 15/01/2021. The data of 205 patients diagnosed with uterine sarcoma who were followed up in our clinic between January 2002-2020 were retrospectively reviewed. Patients who did not undergo surgery in our hospital, the presence of another cancer, and patients with missing data (n=32) were excluded from the study, after which 173 patients were included. The age, surgical and adjuvant treatments, pathological results, follow-up information, treatments given, survival and recurrences of patients were retrieved from the medical records of our hospital. Pathology specimens were reviewed by expert pathologists. Patients were staged according to FIGO 2009. Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) with or without pelvic lymph node dissection (PLND) were performed for all operable patients. Additionally, low anterior resection plus colostomy, pelvic peritoneectomy, implant resection were performed in indicated cases (Table 1).

We categorized the patients according to age and tumor size. A cut-off size of 5 cm was reported in FIGO 2009 staging system. According to this, we grouped patients with tumors below and above 5 cm. For CS there was no consensus regarding tumor diameter. We aimed to analyze whether a cut-off of 5 cm tumor size is a significant factor for outcome. We also categorized the patients as those younger and older than 50 years of age. Since 50 years is a significant factor for endometrial cancers, we aimed to assess whether the same is true for sarcomas as well. Cox regression analysis was used for the comparison of these groups.

Whether the patient was to receive adjuvant radiotherapy (RT), chemotherapy (CT), or combination therapy was decided by the members of the tumor board, depending on the age, stage, lymph node metastasis, medical comorbidities, and performance. Patients were followed up every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually.

Statistical analysis

Statistical analysis was performed with SPSS version 22 (SPSS for Mac Inc., Chicago, IL, USA). P-value <0.05 was considered statistically significant. To identify whether the data were normally distributed, Shapiro-Wilk’s test, histograms, Q-Q plots tests were used. Descriptive statistics were presented as median (SD). Univariate and multivariate cox regression analysis were used to identify factors that affect overall (OS) and disease-free survival (DFS). The Kaplan-Meier method was used to assess survival. Log-rank statistical analyses were used when comparing lifetimes of cases with categoric variables.

Results

The mean age of the patients was 57.6 (11.2) years. Carcinosarcoma (50.9%) and leiomyosarcoma (27.7%) were the most common histopathological types. Most patients had stage 1 disease (n=115, 66.5%), 17 patients had (9.8%) stage 2, 31 (17.9%) had stage 3 and 10 (5.8%) had stage 4 disease (Table 1).

| Table 1: Clinicopathologic features of sarcomas |
|-----------------------------------------------|
| Type                     | n (%) | 95%CI |
|--------------------------|-------|-------|
| LMS                      | 48(27.7%) | 21.4-34.1|
| CS                       | 88(50.9%) | 42.8-58.4|
| ESS                      | 27(15.6%) | 10.4-21.4|
| US                       | 21(1.2%) | (0.2-9.9)|
| AS                       | 8(4.6%)  | 1.7-8.1 |
| Total                    | 173(100%)|       |
| OP                       | n (%)  | 95%CI |
| TAH                      | 2(1.2%) | (0.2-9.9)|
| TAH BSO                  | 59(34.1%)| 27.2-42.2|
| TAH BSO PLND             | 19(11.4%)| 2.9-10.4|
| TAH BSO PPLND            | 30(18.1%)| 7.7-28.9|
| TAH USO                  | 3(1.7%)  | (0.3-5.3)|
| TAH BSO PPLND Low Ant Resc. | 42.3% | 6.8-46.4|
| TAH BSO PPLND Implant Resc. | 10.6% | (0.1-1.7)|
| TAH BSO PLND Pelvic Peritoneectomy | |
| Stage                    |       |       |
| 1                        | 115(66.5%)| 59.5-72.8|
| 2                        | 17(9.8%)  | 5.8-14.5 |
| 3                        | 31(17.9%) | 12.1-23.7|
| 4                        | 10(5.5%)  | 3.9-19.8 |
| Mean                     | (SD)   |       |
| TM Size                  | 6.46   | 3.8    |
| Adjuvant Treatment       | N (%)  | 95% CI |
| Yes                      | 162(92.6%)| 88.7-96.1|
| No                       | 11(6.4%) | 2.9-10.4|
| Mean OS                  | (SD)   |       |
| Adj TX Yes               | 116    | 16.2   |
| Adj TX No                | 168    | 8.7    |
| Mean                     | (SD)   |       |
| Age                      | 57.6   | 59.5-72.8|
| n (%)                    | 95% CI |
| Follow up (Month, Median)| 39     |       |
| Local Recurrence         |       |       |
| Yes                      | 3 (1.7%) | (0.4) |
| No                       | 170(98.3%)| (96-100)|
| Distant Met              |       |       |
| Yes                      | 20(11.6%)| 4.6-21.2|
| No                       | 153(88.4%)| 83.8-93.1|

LMS: Leiomyosarcoma, CS: Carcinosarcoma, ESS: Endometrial stromal sarcoma. US: Undifferentiated sarcoma. AS: Adenosarcoma, 95% CI: 95% Confidence Interval (lower-upper limits), TM Size: Tumor size. OP: Operation. Adj TX: Adjuvant treatment. RT: Radiotherapy. CT: Chemotherapy.

Three patients had local vaginal cuff recurrence and twenty patients (11.6%) had distant metastasis involving the liver, lung, pelvis, paraaortic lymph nodes and groin region. All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH BSO). Only one patient underwent TAH and unilateral salpingo-oophorectomy (USO) due to a former oophorectomy operation. Ninety (52%) patients underwent TAH+BSO and Pelvic (P) and paraaortic (PA) lymph...
node dissection (LND). Among all, 162 (93.6%) received adjuvant therapy, while 11 (6.4%) did not. These patients were all stage I A LMS patients. Mean tumor size was 6.46 (3.8) cm. Local recurrence occurred in three (1.7%) and distant metastasis occurred in twenty patients (11.6%).

The mean age of LMS patients was 53.3 (9.4) years and the mean tumor size was 8.06 (4.9) cm. Thirty-seven (77.1%) LMS patients had stage 1 disease, 6 (12.5%) had stage 2, 1 (2.1%) had stage 3, 4 (8.3%) had stage 4 disease. Out of the forty-eight patients, thirty-seven (77.1%) received adjuvant therapy, 23 (47.9%) patients received RT only, 4 (8.4%) received CT only, 10 (20.8%) patients received both RT and CT. Twenty-five (52.1%) patients underwent TAH BSO, 2 (4.2%) underwent only TAH, 10 (20.8%) patients underwent TAH BSO, P and LND, and 14 (29.2%) underwent TAH BSO, P, PA and LND. Local recurrence was seen in 1 (2.1%) patient while distant metastasis was seen in 9 (18.8%) patients. A mean of 15 (8.7) pelvic lymph nodes and 10 (2.9) paraaortic lymph nodes were dissected. No metastasis was detected among patients who underwent lymph node dissection (Table 2).

Table 2: Clinicopathologic features of LMS

| Feature | n=48 (27.7%) |
| --- | --- |
| Age (mean (SD)) | 53.3 (9.4) |
| Tm Size (mean (SD)) | 8.06 (4.9) |
| Stage | n(%) 95%CI |
| 1 | 37 (77.1%) 64.6-97.5 |
| 2 | 6 (12.5%) 4.2-22.9 |
| 3 | 1 (2.1%) 0.6-3.3 |
| 4 | 4 (8.3%) 2.1-16.7 |
| Adj Treat. | n(%) 95%CI |
| Yes | 37 (77.1%) 64.6-89.6 |
| No | 11 (22.9%) 10.4-34.5 |
| Only RT | 23 (47.9%) 33.3-62.5 |
| Only CT | 4 (8.4%) 2.1-16.7 |
| RT+CT | 10 (20.8%) 8.4-33.3 |
| Op | n(%) 95% CI |
| TAH | 2 (4.2%) 0.4-10.4 |
| TAH BSO | 25 (52.1%) 39.6-66.7 |
| TAH BSO PLND | 5 (10.4%) 2.1-18.8 |
| TAH BSO PPLND | 14 (29.2%) 16.7-41.6 |
| TAH USO | 2 (4.2%) 0.4-10.4 |
| Local Recurrence | 1 (2.1%) 0.6-3.3 |
| Distant Met | 9 (18.8%) 8.3-31.3 |
| Pelvic Lymph Node Number | 15 (32.5%) |
| Number median (SD) | 10 (2.9) |
| Paraaortic Lymph Node Number | 0 |
| Median Number (SD) | 0 |
| Pelvic Lymph Node Met | 0 |
| Paraaortic Lymph Node Met | 0 |

Adenosarcoma (AS) and undifferentiated sarcoma (US) rates were 4.6% and 1.2% respectively. Factors (tumor size, age, recurrence, adjuvant treatments) affecting overall and disease-free survival were evaluated for LMS and CS patients (Table 3 and 5). For OS and DFS, recurrence was a significant prognostic factor in LMS in univariate and multivariate (P<0.05 for all analyses and in CS patients, in multivariate analysis (P=0.02 and 0.01 respectively for OS and DFS analysis).

The mean age and tumor sizes of CS patients were 58.2 (12.2) years and 5.7 (3.3) cm, respectively. Fifty-nine (67.8%) had stage 1 disease, 8 (9.2%) had stage 2 disease, 17 (19.5%) had stage 3 disease and 3 (3.4%) had stage 4 disease. Eighty-nine (90.9%) patients received RT and CT, 8 (9.1%) received CT only, while no patients received RT only. Forty-eight (54.5%) patients underwent TAH BSO, P, PA and LND. Thirty-three (37.5%) patients underwent TAH BSO, P and LND. The mean number of dissected pelvic and paraaortic lymph nodes were 15 (5.4) and 9 (5.7), respectively. Ten (20%) pelvic and three patients (6.3%) had paraaortic lymph node metastasis, while 7 (8%) had distant metastasis (Table 4).

Table 3: Factors affecting overall and disease-free survival in LMS patients

| Feature | Overall Survival | Disease Free Survival |
| --- | --- | --- |
| Tm Size(≤5cm,>5cm) | P-value OR 95%CI | P-value OR 95%CI |
| Age (≤50,>50) | 0.06 0.14 0.19-1.14 0.06 0.14 0.01-1.15 |
| Adjont Therapy | 0.56 0.71 0.22-2.22 0.50 0.68 0.22-2.07 |
| Recurrence (local distant) | 0.00 0.09 0.02-0.35 0.00 0.02 0.00-0.13 |
| Multivariate analysis | Overall Survival | Disease Free Survival |
| P-value OR 95%CI | P-value OR 95%CI |
| Tm Size(≤5cm,>5cm) | 0.06 0.11 0.01-1.13 0.00 0.10 0.01-1.33 |
| Age (≤50,>50) | 0.64 0.75 0.22-2.53 0.38 0.5 0.18-1.91 |
| Adjont Therapy | 0.40 0.50 0.09-2.75 0.98 0.9 0.19-9.44 |
| Recurrence (local distant) | 0.00 0.10 0.02-0.40 0.00 0.03 0.00-0.15 |

The mean age in ESS patients was 62.8 (7.4) years and mean tumor size was 6.3 (2.9) cm. Thirteen (48.1%) patients had stage 1, 2 (7.4%) had stage 2, 10 (37.0%) had stage 3 and 2 (7.4%) had stage 4 disease. Seventeen (63%) patients received RT and CT, 5 (18.5%) received only CT, 5 (18.5%) received progesterone hormone therapy. Twenty-two (81.5%) patients underwent TAH BSO, P, PA and LND, and 2 (7.4%) underwent TAH BSO, P and LND. Local recurrence occurred in 2 (7.4%) patients while distant metastasis was seen in 4 (14.8%). The mean number of dissected pelvic and mean paraaortic lymph nodes were 15 (10.2) and 11 (10.7), respectively. Pelvic and paraaortic lymph node metastases were detected in 9 (36%) and 6 (24%) patients, respectively (Table 6).
Table 6: Clinicopathologic Features of ESS

| Feature                                      | Value   |
|----------------------------------------------|---------|
| Age (mean (SD))                              | 62.8 (7.4) |
| Tm Size (mean (SD))                          | 6.3 (2.9) |
| Stage                                        | 95% CI  |
| 1                                            | 29.6-66.7 |
| 2                                            | 0-18.5  |
| 3                                            | 18.5-55.6 |
| 4                                            | 0-18.5  |
| Adjuvant Treatment                           | 95% CI  |
| m(%)                                         | 3.7-33.5 |
| Hormone                                      | 3.7-33.5 |
| Pelvic Lymph Node Number Median (SD)         | 11 (10.7) |
| Pelvic Lymph Node Met                         | 9 (36%)  |
| Paraortic Lymph Node Met                     | 6 (24%)  |

95% CI: 95% Confidence Interval (lower-upper limits), TM Size: Tumor size, OP: Operation, ADJ TREAT: Adjuvant treatment, RT: Radiotherapy, CT: Chemotherapy

The median overall survival (OS) was 39 (range 3-214 months) months. All patients were followed-up for 200 months, during which 22 patients died. The 200-month OS rate of all patients was 60.9% (Figure 1). The patients were evaluated with respect to the diagnoses (Figure 2). Sarcoma type had no significant impact on OS (P=0.13). The mean OS in patients who did and did not receive adjuvant treatment were 116 (16.2) months and 168 (8.7) months, respectively (Table 1). The patients were evaluated with respect to the stages and adjuvant treatment. While early stages had a significant impact on OS (Figure 3), adjuvant treatment did not (P<0.001 and P=0.50, respectively) (Figure 4).

Discussion

Uterine sarcomas are rare and aggressive gynecological tumors with poor prognosis. Our results demonstrated that CS is the most common type of sarcoma in our clinic. Compared to other groups of sarcomas, none of the sarcoma diagnosed patients had significantly worse overall survival. The rate of LMS and CS among all uterine sarcomas were reported as 40% and 40%, respectively [5]. In the present study, the rates of LMS and CS were 27.7% and 50.9%, respectively.

Leiomyosarcomas are highly aggressive tumors and rare entities with a poor and unfavorable prognosis. The recurrence rate ranges from 53% to 71% [3]. In this study, local recurrence and distant metastasis occurred in 2.1% and 18.8% of the patients, respectively. LMS may result from a sarcomatous transformation of a leiomyoma [6]. The basis of the therapy is total abdominal hysterectomy and debulking of any extrauterine tumor. For early stage leiomyosarcoma, the incidence of lymph node metastasis is rare, therefore lymphadenectomy is not recommended [7]. In the present study, 10.4% of patients underwent TAH BSO, P and LND and 29.2% patients underwent...
TAH BSO, P, PA, and LND. Metastasis was not detected in any of the patients who underwent lymph node dissection.

The effect of adjuvant therapies on survival is controversial [8]. Several studies have found that radiation therapy improved local control but had no significant impact on OS [9]. In the present study, 47.9% of leiomyosarcoma diagnosed patients received only RT, 8.4% received only CT and 20.8% received both RT and CT. Among those who received RT, 2.1% had local recurrence. On the other hand, in this study, adjuvant treatment had no impact on OS.

Tumor size and mitotic index were reported as prognostic factors [3,10]. Stage is considered the most important prognostic factor for uterine sarcomas. In the present study, tumor size, age, and adjuvant treatments (RT, CT, or both) had no significant impact on OS and DFS in both univariate and multivariate cox regression analysis. However, for LMS patients, recurrence had a significant impact on survival in univariate and multivariate analyses.

Carcinosarcomas are rare tumors. They are considered a variant of high-risk endometrial adenocarcinoma [11] and arise from the endometrial tissue of the uterus. However, endometrial sampling may not be an accurate test for the diagnosis of uterine carcinosarcoma [12]. Carcinosarcomas mostly occur in elderly patients. Similarly, in our study, the median age was 58.2 (12.2) years. For surgical staging, total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH BSO), pelvic and para-aortic lymph node dissection, and pelvic lavage are required. In one study, the median survival with and without lymphadenectomy was 54 and 25 months [13]. Ferguson et al. reported that 10% of carcinomatous components were grade I, 10% were grade II, and 80% were grade III [14].

In our study, 88 (50.9%) patients had carcinosarcoma, twice as much as the number of LMS patients [48(27.7%)]. Like endometrial carcinomas, stage and the depth of the myometrial invasion are the most important prognostic factors. Serous and clear cell carcinoma components tend to metastasize more. In our study, recurrence was the only significant prognostic factor in multivariate analysis of CS patients.

Endometrial stromal sarcomas (ESS) are exceedingly rare tumors. The percentage of ESS is approximately 7–25% in all uterine sarcomas [15]. In the present study, 15.6% of all sarcoma patients were diagnosed with ESS. Endometrial stromal tumor (ESS) cells resemble endometrial stromal cells of the proliferative endometrium. ESS can be divided into 3 subgroups: Endometrial stromal nodule, low grade endometrial stromal sarcoma (LG-ESS), and high-grade endometrial sarcoma [16]. ESS typically develops in perimenopausal women with a mean age of 46 years (range: 18–83 years) [17]. In this study, the mean age was 62.8 (7.4) years. Abeler et al. [3] reported that prognosis of endometrial stromal sarcoma confined to the uterus was related to mitotic index and tumor cell necrosis. The risk of recurrence in LG-ESS is 10–20%, and late recurrences are characteristic of the disease [18]. LG-ESS have high levels of steroid receptors and these tumors can metastasize from the uterus to the ovaries. Five of our LG-ESS diagnosed patients received progesterin therapy and local and distant metastases occurred in 2 (7.4%) and 4 (14.8%) patients, respectively. The reported pelvic lymph node metastasis in CS and ESS is about 15% [19]. However, in our study, 36% of ESS diagnosed patients had pelvic and 24% had paraaortic lymph node metastasis. ESS requires the same extended surgical staging as endometrial adenocarcinoma. We had eight patients with adenocarcinoma.

This study is not free of bias. First, these results represent the experience of a single center and do not give us the opportunity for a head-to-head comparison with other centers. Second, experience and training of surgeons may differ globally and the outcomes may differ accordingly. Despite these potential biases, single center experience allowed us to define a more homogeneous surgical technique to compare the outcomes with respect to different patient characteristics.

In the literature, there is a little evidence that supports the use of adjuvant chemotherapy for sarcomas, except for CS. On the other hand, Terek et al. reported that adjuvant chemotherapy is a significant prognostic factor for survival in uterine sarcomas [20].

Limitations
The main limitation of this study is its retrospective design. Since we did not design an experimental prospective study, sample size calculation was not performed prior to analysis. Additionally, sarcomas are rare tumors and the design of a prospective study with a-priori sample size calculation was not feasible. Larger prospective series and meta-analysis evaluating global results are needed to further evaluate uterine sarcomas.

Conclusion
As in all cancers, early stage is an important prognostic factor for all sarcoma types. Tumor size, age and adjuvant treatments had no significant impact on survival. Although the data is limited about ESS, based on our results, ESS requires extended surgical staging as well as CS. However, further clinical studies are needed for the surgical and adjuvant treatment decisions of uterine sarcomas.

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