Original Articles

Prognostic factors, survival outcomes and surgical practices when dealing with uterine sarcomas: 8 years of clinical experience

Meseci and Naki. Uterine sarcomas

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Abstract
Objective: To determine clinical and pathological characteristics, prognostic factors, surgical practice, adjuvant therapies, and survival outcomes of uterine sarcoma cases diagnosed and treated in our institution.
Material and Methods: Patients diagnosed and treated for uterine sarcomas at our institution from 2009 to 2017 were retrospectively evaluated. All histological slides from the specimens underwent a thorough pathological review by a gynecological pathologist. The following variables were assessed: age, family history of cancer, smoking status, age of menarche, parity, age at first delivery, related symptoms, clinical staging, histological type, treatment received, disease-free period (DFP), and time and site of recurrence, as well as treatment of the latter and overall survival (OS).
Results: Ten patients were diagnosed with leiomyosarcoma (LMS), a further ten patients had Malignant Mixed Müllerian tumors (MMMT), while five had endometrial stromal sarcoma (ESS) with the other nine having other tumors. At the end of our study 12 (35.3%) patients were alive and in remission, 4 (11.8%) were alive with disease, 10 (29.4%) were lost to follow-up and 8 (23.5%) had died. Mean survival time was 80.92 months, and 2-year survival rate was 75.6%. We found that survival was significantly shorter in the presence of lymph node involvement, residual tumor and recurrence.
Conclusion: This study serves to inform clinicians about the outcome of various uterine sarcoma's which were diagnosed and managed at our center. We have found that 35.3% of our patients were alive and in remission, 11.8% were alive with disease, 29.4% were lost to follow up, while 23.5% of patients having died.
Keywords: Carcinosarcoma, leiomyosarcoma, prognosis, sarcoma, survival

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Introduction

Uterine sarcomas are malignant tumors that originate from the mesodermal tissues (muscle and supportive tissues) of the uterus. They are usually of heterogeneous characteristic and represent a small group among the malignant neoplasms of the uterus [1, 2]. The prevalence of uterine sarcoma is between 1.5 and 3 cases per 100000 for Caucasians and Afro-Americans, respectively [3].
The World Health Organization (WHO) classifies uterine sarcomas into two types: (1) malignant mesenchymal tumors and (2) mixed epithelial and mesenchymal tumors. Pure mesenchymal tumors are further subclassified as leiomyosarcoma (LMS), low- and high-grade endometrial stromal sarcomas (LG-ESS and HG-ESS, respectively) and undifferentiated uterine sarcoma (UUS) [4]. Among these, LMS is the most frequently seen type with a frequency of 60–70% among all uterine sarcomas; while the remaining 3 subtypes (LG-ESS, HG-ESS and UUS) collectively comprise another 10% of uterine sarcomas [5]. Mixed tumors are comprised of adenosarcoma (AS), rhabdomyosarcoma (RMS), and perivascular epithelioid cell neoplasms (PEComa) [4, 6]. These are much more rare, collectively representing around 5% of all uterine sarcomas [7].
Although dependent on tumor type, uterine sarcomas are most commonly seen between the 5th and 7th decade of life. Risk factors for uterine sarcoma development have been identified as obesity, diabetes, having undergone previous pelvic irradiation therapy and/or tamoxifen treatment, and having excessively high or unopposed estrogen levels[8-12]. However, data is scarce on this topic due to the rarity of uterine sarcomas; therefore, there is no universal consensus on risk factors, optimal therapeutic approaches, and the frequency of poor outcomes. Our aim in this study was to determine the clinical/pathological characteristics, prognostic factors, surgical practices, adjuvant therapies, and survival outcomes of patients who received treatment for uterine sarcoma at our institution.

Materials and methods

Our study was a retrospective evaluation of the medical files of patients who were diagnosed with uterine sarcomas and treated at our institution from 2009 to 2017. The study was approved by the local Ethical Committee (reference number: 2017-16/28). All histological slides underwent a thorough pathological review by a gynecological pathologist. Staging was performed according to the current International Federation of Gynecology and Obstetrics (FIGO) criteria [13].

Our patient group also included those who had been diagnosed with uterine carcinosarcomas (also called Malignant Mixed Müllerian Tumors, MMMT), as these tumors are now classified within the uterine carcinoma group (they were previously considered as uterine sarcomas) [14, 15].Also of note, 4 patients in which endometrial sampling had not detected malignancy, but hysterectomy results were conclusive of uterine carcinoma (1 LMS, 1 MMMT, 1 LG-ESS, 1 AS) were also included in the study. Two patients who were initially diagnosed with LG-ESS, but were found to have endometrial stromal nodule and high-grade serous carcinoma after hysterectomy, were excluded from the study. Patients with metastatic sarcoma from other gynecological sites and those who had incomplete data for demographic analyses were excluded from the study altogether.

All remaining patients who were confirmed to have uterine sarcomas were included in the study; however, those without sufficient data in terms of clinical findings, pathological results, follow-up studies and treatment approach/results were excluded from the survival analysis.The following characteristics of all patients were assessed and recorded: age, parity, age at first delivery, age at menarche, family history of cancer, smoking status, and other related symptoms. In regard to disease characteristics, the following were assessed from medical records: clinical stage, histological type, treatment approach, disease-free period (DFP), overall survival (OS), and the time and site of recurrence.

Patients were grouped according to the following parameters: tumor size (≤5 cm, >5 cm), FIGO stage (early (I-II), advanced (III-IV)), histological grade (low, moderate, high), myometrial invasion (absent, <50%, ≥50%). In addition, Ki-67 positivity was also evaluated on a present/absent basis with a cut-off of 14%.

The treatment plan of each patient was structured according to the most recent protocols and guidelines with regard to tumor stage/grade, age and cell type. The use of adjuvant therapies such as chemotherapy, radiotherapy or immunotherapy were also based on most recent guidelines. All surgical interventions were carried out by our Gynecology Department and lymphadenectomies were performed according to the discretion of the primary surgeon in each operation.

Disease free survival was defined as the period of time (in months) from diagnosis to either recurrence or last follow-up. Overall survival was defined as the period of time (also in months) between diagnosis to either date of death or last follow-up.

Statistical Analysis

All statistical analyses were performed on SPSS version 21 software for the Windows operating system (IBM, Armonk, NY, USA). Continuous variables are given as mean ± standard deviation (SD), while categorical variables are presented with frequency (n) and percentage (%). The DFS and OS analyses were performed with the Kaplan-Meier method. The comparison of survival times between groups were performed with the Log-Rank test. Cox-regression analysis with the Backward conditional method was utilized to determine the effects of continuous and categorical variables on survival times. P values lesser than 0.05 were accepted to show statistical significance.

Results

The mean age of the 34 patients included into our study was 52.56 ± 14.47 years. Ten patients had LMS, 10 patients had MMMT, 5 patients had ESS, while 9patients had other type of tumors (5 with AS, 3 with UUS, 1 with embryonal rhabdomyosarcoma). Patients with MMMT were found to have higher mean age compared to the other groups (62.40 ± 7.97 years compared to 49.80 ± 5.87 years in LMS, 39.60 ± 13.22 years in ESS, and 51.89 ± 20.74 years in other sarcomas). Age difference was only significant when the MMMT and ESS groups were compared (p=0.016). Mean follow-up duration of the patients was 31.1 ± 31.1 months.

FIGO staging revealed that 22 patients (64.7%) were stage I, 7 patients (20.6%) were stage II, 1 patient (2.9%) was stage III, 4 patients (11.8%) were stage IV. The majority of our patients (67.6%) were post-menopausal and had presented with bleeding (73.5%). Median primary tumor size was 6 cm (min-max: 2–15 cm). There were no significant differences between the groups in regard to tumor size (p=0.845). 19 patients had undergone pelvic and/or paraaortic lymph node dissection and only 1 patient (in the MMMT group) was found to have a positive lymph node. 19 (55.9%) patients received at least one kind of adjuvant therapy: 6 received adjuvant chemotherapy, 5 received radiotherapy, 2 received hormonotherapy, while 6 received chemotherapy and radiotherapy in sequence. The most common chemotherapy drugs used were “Carboplatin + Paclitaxel”. Three patients were found to have residual tumor after surgery, while 14 patients had recurrence. The pelvic peritoneum was the most common site of recurrence in this patients. At final follow-up, 12 (35.3%) patients were alive and in remission, 4 (11.8%) were alive with disease, 10 (29.4%) had been lost to follow-up and 8 (23.5%) had died (Table 1).

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Mean DFS was 61.21 ± 11.11 months (Figure 1). Disease free survival was significantly higher for patients with early FIGO stages (p=0.030). Tumors with high histologic grade had lower disease-free survival times compared to the low and moderate grades (p=0.005) (Figure 2). We found that DFS was significantly decreased in cases with lymphovascular involvement (p=0.015) and those with of positive lymph nodes (p<0.001). We also found that those with residual tumor and positive Ki-67 indexes had lower disease free survival; however, these results were not found to be significant. Receiving adjuvant therapy was found to have no significant effect on disease free survival (p=0.490) (Table 2).
Mean survival time was 80.92 ± 11.46 months and 2-year survival rate was 75.6% (Figure 3). Survival times were significantly lower in patients who were found to have positive lymph nodes (p=0.048), those with residual tumor (p<0.001) and those with recurrence (p=0.004) (Figure 4). We also found that patients with at least one parity, early (FIGO I and II) stages, and low histological grade had higher survival times overall, but these results were not statistically significant (Table 3).
Having performed the Cox-Regression Analysis, we found that age and parity had no significant effect on disease free survival times. However, those who were older at menarche had 2.2-times higher risk for recurrence and those who were older at first delivery were found to have 1.9-fold greater risk for recurrence. Additionally, larger tumor size also incurred a 1.5-fold higher (for each cm) risk for recurrence (Table 4). We found no significant effect on survival rates when we took into account age, age at menarche, age at first delivery (Table 5). Furthermore, we found larger tumor sizes to decrease survival rates but this result deemed statistically insignificant.

Discussion

Uterine sarcoma is rare and difficult to study; therefore, it features very little in the current medical literature. The study herewith is made up of 34 patients being referred over an 8-year period.
Histopathological evaluations revealed that LMS and MMMT occurred in equal frequency in our group of patients (29.4%); this was followed by ESS (14.7%). Our data is comparable to some studies [7, 16] but at the same time there are studies reporting very different histopathological distributions in their results [17-19]. It should be noted that small numbers of cases and changes in the WHO classification in each study may have caused these differences.
The mean age of our patients were 62.4 years in those with MMMT, 49.8 years in those with LMS, 39.6 years in those with ESS, and 51.8 years in other type sarcomas. Our findings were consistent with the study by Benito and Potikul, with the only exception being the ESS group, which was younger in our study [17, 18].
In the current study, only 7 cases of uterine sarcoma were diagnosed in patients under 40 years old and the majority of cases were seen in postmenopausal women. Although RMS is usually associated with the pediatric age group[20], one patient was diagnosed at age 31. Another patient's diagnosis was made during cesarean section by ovarian biopsy which revealed a high grade UUS. At time of diagnosis, metastases had already developed in the lung, brain and liver.
One patients had a personal history of breast cancer, while four had concomitant malignancies associated with MMMT: 1 gastrointestinal stromal tumor, 2 low grade uterine endometrioid adenocarcinomas and 1 high grade ovarian serous adenocarcinoma.
Family history for cancer was positive for a total of 6 (17%) patients, with breast carcinoma being the most commonly reported type. None of the patients had a personal or family history of sarcoma, nor did they report any history of pelvic irradiation. One patient (2.9%) who had a prior history of breast carcinoma had received treatment with tamoxifen. Durnalı et al. reported tamoxifen treatment frequency as 1% in their study [21]. Benito et al. reported a higher incidence of a positive family history (40.4%), while prior history of cancer was similar to that reported by Benito et al. and Koivisto-Korander in their studies (10.1% and 11%, respectively) with breast carcinoma as the most common. Similar to our study, these studies also reported that none of their patients had a history of pelvic irradiation [17, 22]. Wais and Durnalı reported a lower occurrence of personal cancer history among their patients (8%, 3%, respectively) and a history of pelvic irradiation was reported in only 1% [19, 21].
A correct preoperative malignancy diagnosis was achieved in 17 of our patients (73.9%). Some studies have reported higher (86–88%) rates of preoperative diagnosis, while others have reported lower rates (65%, 64%) [18, 19, 23]. Bansal et al. correctly predicted the presence of invasive tumors in 86%, while also correctly predicting the histologic subtype in 64% of their patients [23]. Some differences in the preoperative diagnostic method may have resulted in variable results.
In this patient group, complete resection of the uterus and removal of both adnexa is the widely accepted approach to treatment of early-stage disease. It is suggested to avoid pelvic and para-aortic lymphadenectomy when unremarkable, except for cases with MMMT [5]. In cases with MMMT limited to the uterus, positive lymph nodes are reported in around 30% of patients. The literature on this topic reports that OS is adversely effected by systematic lymph node involvement [5]. In our study, we found that the mean number of lymph nodes that were removed was 18.9±22.4; this value was 15.1±17.4 for pelvic lymph nodes and 12.6±9.2 for

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paraaortic lymph nodes. According to pathology reports, one of the pelvic lymph nodes demonstrated high grade MMMT (FIGO 3C). Overall survival time of this patient was 12 months. However, the literature on this topic reports higher lymph node metastasis rates. In the current study, lymph node metastases were not found in any of the patients with other types of sarcomas. The number of patients with positive lymph nodes was low in our study, and survival times were found to be significantly lower for those with positive lymph nodes.

In patients with LMS limited to the uterus, the ovaries of women of childbearing age may be preserved [24, 25]. Additionally, preservation of the ovaries was not found to impact overall survival negatively in patients with LG-ESS; however, it is crucial to consider removal of ovaries on a case-by-case basis as LG-ESS is known to be an endocrine-driven tumor [26]. The preservation of ovaries was performed in only 5 patients in the current study. One of these patients had AS and underwent TAH + BPLND, but was later (6 months) found to have adnexal metastasis. The lesion was subsequently excised and palliative chemotherapy was recommended. Eighteen months after the initial treatment she was lost to follow up, as she had settled overseas. Another patient had botryoidal type embryonal rhabdomyosarcoma (ERMS), at the time of diagnosis and was pregnant. She gave birth through cesarean section at 35 weeks of gestation after confirmation of fetal lung maturation, and later underwent radical hysterectomy + BPPALND + oophoropexy with postoperative adjuvant chemotherapy (vincristine and actinomycine D). She is still alive without any evidence of disease at 105 months of follow up. Two patients who had had undergone hormone therapy were still alive at 16 and 121 months of follow-up. Brain metastasis occurred at the seventh month in a patient with LMS whilst receiving chemotherapy with the survival time being months. Due to the limited number of patients, it is difficult to make any recommendation for ovarian preservation.

In our study most patients were diagnosed at early stage (85.3% were diagnosed at FIGO stages I and II). This is higher compared to other studies which reported rates between 58–66% for early stage disease diagnosis [17, 18, 21, 22]. In contrast to our results, MMMT was most often diagnosed during advanced stages [17, 18, 21]. However, in our study, only 20% of MMMT cases were detected at the advanced stage. These differences may be explained by the extent of the operative procedure, the extent and type of sarcoma, and the newer FIGO staging system we have used. Given these differences, it may not be feasible to compare our study with the prior studies on this field.

In patients with uterine sarcomas, the role of adjuvant therapy on survival is uncertain [7]. Studies show that adjuvant chemotherapy has a positive effect on survival in MMMT and LMS (increasing OS and DFS), while receiving pelvic irradiation was associated with significantly higher overall survival in those with ESS and UUS [27, 28]. In a large study comprised of 3650 patients with uterine sarcoma (MMMT, ESS, LMS and UUS), it was shown that adjuvant pelvic radiotherapy had reduced local-regional failure in up to 53% of the cases [29]. Durnali et al. showed that adjuvant radiotherapy after chemotherapy for uterine sarcomas improved DFS but had no effect on OS [21]. In our present study, adjuvant therapy did not seem to improve OS. However, due to the low number of patients in our study, it would be unfeasible to draw conclusions in regard to the efficacy of adjuvant treatments. Uterine sarcomas have a poor prognosis overall. Our results show the recurrence rate to be 41.1% for patients with uterine sarcoma with a median follow-up time of 61.2 months. Previous reports of recurrence rates have been reported to range between 36% and 63.4% [16-18, 21, 30]. In the current study, the following factors were found to contribute to significantly poor prognosis: later FIGO staging, higher tumor grade, LVSI and lymph node involvement. We also found that presence of residual tumor and positive Ki-67 decreased DFS; however, the decreases were not statistically significant for either comparison, presumably due to the low number of patients. However, our findings were in agreement with a few previous studies [18, 30]. It should also be mentioned that higher age at menarche and higher age at first birth were associated with recurrence, which are strongly considered as being risk factors for UUS [31].

Mean OS in our study was found to be 80.92 months, while the 2-year survival rate was 75.6%. In previous studies 2-year OS has been reported within a range of 49-69%, while 5 year OS is reported between 45-59% [16, 17, 21, 30]. According to our results, survival times were significantly lower in those with lymph node involvement, residual tumor and tumor recurrence. We also found that patients with at least one parity, early FIGO (I & II) stages and low histological grade had longer survival.

Limitations to our study: Firstly, it is rather evident that our findings should be interpreted in the context of the limitations associated with retrospective studies. Secondly, the number of cases was low; however, uterine sarcomas are rare and the fact that the study was carried out in a single center with rigorous inclusion/exclusion criteria further limited the number of patients that could be included in the study. Lastly, the number of patients lost to follow-up due to various reasons can be considered as another limitation of the study. In regard to these limitations, our results concerning the survival of these patients must be evaluated with caution.

In conclusion, at the final follow-up of the current study, 35.3% of patients were alive and in remission, 11.8% were alive with disease, 29.4% were lost to follow-up and 23.5% had died. Mean survival time was 80.92 months and the 2-year survival rate was found to be 75.6%. According to our results, survival times were significantly lower with lymph node involvement, presence of residual tumor and tumor recurrence. We also found that patients with at least one parity, early FIGO stages (I & II) and low histological grade had higher

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survival times. Considering the low incidence of uterine sarcomas and because of the recent changes in the classification system, it is very difficult to reach conclusions in terms of treatment strategies.

Ethics Committee Approval: Ethics approval (reference number: 2017-16/28) was given by the Local Ethic Committee of *** University.
Informed Consent: Informed consent was not taken due to retrospective study design.
Peer-review: Externally peer-reviewed.
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Table 1. Summary of Our Variables

	All Patients (n=34)	LMS (n=10)	MMMT (n=10)	ESS (n=5)	Others (n=9)	p
Age	52.56 ± 14.47	49.80 ± 5.87	62.40 ± 7.97	39.60 ± 13.22	51.89 ± 20.74	0.021
Family History	9 (26.5%)	4 (40.0%)	1 (10.0%)	2 (40.0%)	2 (22.2%)	0.409
Smoker	8 (23.5%)	2 (20.0%)	4 (40.0%)	1 (20.0%)	1 (11.1%)	0.497
Age at Menarche	11.53 ± 1.52	11.40 ± 0.97	11.60 ± 1.58	11.40 ± 1.67	11.67 ± 2.06	0.979
Age of Menopause	49.30 ± 2.53	48.17 ± 1.60	49.80 ± 2.97	49.00 ± 1.41	49.80 ± 2.95	0.641
Parity						
0	8 (23.5%)	2 (20.0%)	1 (10.0%)	4 (80.0%)	1 (11.1%)	
1	4 (11.8%)	2 (20.0%)	0 (0.0%)	0 (0.0%)	2 (22.2%)	0.090
2	13 (38.2%)	4 (40.0%)	6 (60.0%)	0 (0.0%)	3 (33.3%)	
≥ 3	9 (26.5%)	2 (20.0%)	3 (30.0%)	1 (20.0%)	3 (33.3%)	
Age at First Delivery	22.19 ± 3.16	23.00 ± 2.62	21.89 ± 3.37	20.00 ± 0.00	22.0 ± 3.78	0.795
Menopause Status						
Non-menopausal	11 (32.4%)	4 (40.0%)	0 (0.0%)	3 (60.0%)	4 (44.4%)	0.060
Menopausal	23 (67.6%)	6 (60.0%)	10 (100.0%)	2 (40.0%)	5 (55.6%)	
Body Mass Index	26.33 ± 4.10	25.63 ± 3.25	28.92 ± 4.70	24.10 ± 3.26	25.46 ± 3.79	0.098
Chronic Disease	18 (52.9%)	5 (50.0%)	7 (70.0%)	2 (40.0%)	4 (44.4%)	0.615
Tumor Size	6 (2 – 15)	5.75 (2 – 15)	6 (4 – 8)	5.4 (3 – 11)	4.7 (2 – 13)	0.845
Symptoms						
Bleeding	25 (73.5%)	5 (50.0%)	9 (90.0%)	3 (60.0%)	8 (88.9%)	
Pain	7 (20.6%)	4 (40.0%)	1 (10.0%)	2 (40.0%)	0 (0.0%)	0.082
Detected Incidentally	2 (5.9%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	
Preop Bx						
Benign	6 (26.1%)	1 (16.7%)	2 (22.2%)	1 (50.0%)	2 (33.3%)	0.776

Malign	17 (73.9)	5 (83.3%)	7 (77.8%)	1 (50.0%)	4 (66.7%)	
Preop Tumor Marker						
Positive	3 (8.8%)	0 (0.0%)	3 (30.0%)	0 (0.0%)	9 (100.0%)	0.048
Negative	31 (91.2%)	10 (100.0%)	7 (70.0%)	5 100.0%)	0 (0.0%)	
FIGO Stage						
I	22 (64.7%)	8 (80.0%)	5 (50.0%)	3 (60.0%)	6 (66.7%)	
II	7 (20.6%)	1 (10.0%)	3 (30.0%)	2 (40.0%)	1 (11.1%)	
III	1 (2.9%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0.650
IV	4 (11.8%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	2 (22.2%)	
Histologic Grade						
Low	7 (21.2%)	1 (10.0%)	0 (0.0%)	4 (80.0%)	2 (25.0%)	
Moderate	8 (24.2%)	3 (30.0%)	2 (20.0%)	0 (0.0%)	3 (37.5%)	0.016
High	18 (54.5%)	6 (60.0%)	8 (80.0%)	1 (20.0%)	3 (37.5%)	
Myometrial Invasion						
Absent	7 (24.1%)	2 (25.0%)	2 (22.2%)	2 (66.7%)	1 (11.1%)	
< 50%	12 (41.4%)	5 (62.5%)	2 (22.2%)	0 (0.0%)	5 (55.6%)	0.202
≥ 50%	10 (34.5%)	1 (12.5%)	5 (55.6%)	1 (33.3%)	3 (33.3%)	
Mitotic Index						
Positive	10 (29.4%)	9 (90.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	0.006
Negative	24 (61.6%)	1 (10.0%)	10 (100.0%)	5 (100.0%)	8 (88.9%)	
Lymphovascular Involvement	13 (41.9%)	3 (33.3%)	5 (50.0%)	2 (40.0%)	3 (42.9%)	0.908
Lymph Node Status						
Positive	1 (2.9%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	
Negative	18 (53.0%)	5 (50.0%)	6 (60.0%)	3 (60.0%)	4 (44.4%)	0.613
No Lymphadenectomy	15 (44.1%)	5 (50.0%)	3 (30.0%)	2 (40.0%)	5 (55.6%)	
Adnexa Involvement	6 (18.8%)	1 (10.0%)	3 (30.0%)	1 (20.0%)	1 (14.3%)	0.699
Cervical Involvement	7 (21.9%)	2 (20.0%)	4 (40.0%)	1 (20.0%)	0 (0.0%)	0.271
Omental Involvement	2 (9.5%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0.219
Pelvic Wash						
Positive	1 (2.9%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	
Negative	18 (52.9%)	4 (40.0%)	6 (60.0%)	2 (40.0%)	6 (66.7%)	0.613
Not Applied	15 (44.1%)	6 (60.0%)	3 (30.0%)	3 (60.0%)	3 (33.3%)	
Residual Tumor						
Present	3 (12.5%)	1 (14.3%)	1 (12.5%)	0 (0.0%)	1 (20.0%)	0.838
Absent	21 (87.5%)	6 (85.7%)	7 (87.5%)	4 (%100.0)	4 (80.0%)	
Adjuvant Therapy						
Not Done	15 (44.1%)	6 (60.0%)	4 (40.0%)	1 (20.0%)	4 (44.4%)	
Chemotherapy	6 (17.6%)	2 (20.0%)	2 (20.0%)	0 (0.0%)	2 (22.2%)	
Radiotherapy	5 (14.7%)	1 (10.0%)	2 (20.0%)	1 (20.0%)	1 (11.1%)	0.246
Chemotherapy + Radiotherapy	6 (17.6%)	1 (10.0%)	2 (20.0%)	1 (20.0%)	2 (22.2%)	
Hormonotherapy	2 (5.9%)	0 (0.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	
Chemotherapy						
Not Done	19 (61.3%)	5 (62.5%)	6 (60.0%)	4 (80.0%)	4 (50.0%)	
Vinorelbine+Gemsitabin	1 (3.2%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Carboplatin+Paclitaxel	6 (19.4%)	0 (0.0%)	4 (40.0%)	1 (20.0%)	1 (12.5%)	0.533
Doxorubicin	2 (6.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Dactinomycin+ Vincristine	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Other Multiagent Regimens	2 (6.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	

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Radiotherapy						
Not Done	20 (64.5%)	6 (75.0%)	6 (60.0%)	3 (60.0%)	5 (62.5%)	
Brachytherapy	3 (9.7%)	0 (0.0%)	1 (10.0%)	1 (20.0%)	1 (12.5%)	0.889
Pelvic RT	5 (16.1%)	1 (12.5%)	2 (20.0%)	0 (0.0%)	2 (25.0%)	
Brachytherapy + Pelvic RT	3 (9.7%)	1 (12.5%)	1 (10.0%)	1 (20.0%)	0 (0.0%)	
HRT	2 (5.9%)	0 (0.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	0.006
Recurrence	14 (41.2%)	6 (60.0%)	5 (50.0%)	1 (20.0%)	2 (22.2%)	0.257
Site of Recurrence						
Pelvic Periton	6 (42.9%)	2 (33.3%)	3 (60.0%)	0 (0.0%)	1 (50.0%)	
Lung	3 (21.4%)	1 (16.7%)	1 (20.0%)	1 (100.0%)	0 (0.0%)	0.486
Others	5 (35.7%)	3 (50.0%)	1 (20.0%)	0 (0.0%)	1 (50.0%)	
ki-67						
Positive	16 (47.1%)	7 (70.0%)	3 (30.0%)	2 (40.0%)	5 (55.6%)	0.333
Negative	18 (52.9%)	3 (30.0%)	7 (70.0%)	3 (60.0%)	4 (44.4%)	
Follow-up						
Alive, Remission	12 (35.3%)	2 (20.0%)	3 (30.0%)	4 (80.0%)	3 (33.3%)	
Alive with Disease	4 (11.8%)	1 (10.0%)	3 (30.0%)	0 (0.0%)	0 (0.0%)	0.263
Lost to Follow-up	10 (29.4%)	4 (40.0%)	2 (20.0%)	0 (0.0%)	4 (44.4%)	
Death	8 (23.5%)	3 (30.0%)	2 (20.0%)	1 (20.0%)	2 (22.2%)	

Abbreviations: LMS, leiomyosarcoma; MMMT, malignant mixed mullerian tumor; ESS, endometrial stromal sarcoma; Preop Bx,preoperative biopsy; FIGO,International Fenderation of Obstetrics and Gynecology;HRT,Hormone replacement therapy; RT,Radiotherapy

Uncorrected Proof

Table 2. Disease Free Survival Times (Months) with Kaplan Meier Method and Comparisons of Groups with Long Rank Test For Categorical Variables

	n	Recurrence	Mean	Std Error	%95 Confidence Interval		p
					Lower	Upper	
Disease Free Survival	34	14	61.21	11.11	39.42	82.99	N/A
Smoking Status							
Smoker	8	3	41.67	12.41	17.35	65.98	0.802
Non-smoker	26	11	58.85	12.88	33.60	84.11	
Menopause Status							
Non-menopausal	11	3	86.60	16.42	54.41	118.79	0.184
Menopausal	23	11	30.16	6.03	18.35	41.98	
Chronic Disease							
Present	18	7	32.65	7.42	18.11	47.20	0.748
Absent	16	7	69.92	14.14	42.21	97.62	
Tumor Size							
≤ 5 cm	12	3	85.06	16.94	51.85	118.26	0.076
> 5 cm	22	11	29.67	6.11	17.67	41.63	
FIGO Stage							
Early (I - II)	29	11	66.87	11.79	43.76	89.98	**0.030**
Advanced (III - IV)	5	3	9.40	1.95	5.58	13.22	
Histologic Type							
Leiomyosarcom	10	6	34.88	9.51	16.24	53.53	
MMMT	10	5	22.10	8.91	4.64	39.56	0.284
ESS	5	1	50.60	9.30	32.37	68.83	
Others	9	2	85.11	21.38	43.20	127.03	
Histologic Grade							
Low	7	1	99.00	17.15	65.39	132.61	
Moderate	8	1	91.00	12.97	65.60	116.41	**0.005**
High	18	12	21.89	6.61	8.95	34.84	
Myometrial Invasion							
Absent	7	4	27.86	10.18	7.91	47.80	
< 50%	12	6	49.16	17.33	15.19	83.13	0.186
≥ 50%	10	1	93.67	10.69	72.72	114.61	
Lenfovascular Involvement							
Present	13	9	26.17	12.11	2.43	49.91	**0.015**
Absent	18	5	81.92	13.82	54.83	109.00	
Lenf Nodes Status							
Positive	1	1	3.00	0.00	3.00	3.00	**<0.001**
Negative	18	9	50.16	11.97	26.71	73.61	
Residual Tumor							
Present	3	1	9.00	0.71	7.61	10.39	**0.682**
Absent	21	9	39.01	7.78	23.75	54.26	
Adjuvant Therapy							
Yes	19	9	48.77	12.69	23.90	73.63	0.490

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No	15	5	71.23	16.14	39.60	102.87	
ki-67							
Positive	16	9	31.05	7.95	15.47	46.62	**0.144**
Negative	18	5	80.67	14.32	52.61	108.72	

FIGO,International Fenderation of Obstetrics and Gynecology; MMMT, malignant mixed mullerian tumor; ESS, endometrial stromal sarcoma

Uncorrected Proof

Table 3. Survival Times (Months) with Kaplan Meier Method and Comparisons of Groups with Long Rank Test For Categorical Variables

	n	Death	Mean	Std Error	%95 Confidence Interval		2-years Survival Rate (%)	p
					Lower	Upper		
Overall Survival	34	8	80.92	11.46	58.47	103.38	75.6 ± 9.0	
Smoking Status								
Smoker	8	2	51.17	11.80	28.05	74.29	62.5 ± 21.3	0.986
Non-smoker	26	6	80.85	13.33	54.74	106.97	80.7 ± 8.9	
Menopause Status								
Non-menopausal	11	2	98.00	13.99	70.57	125.43	79.5 ± 13.1	0.371
Menopausal	23	6	52.21	9.71	33.18	71.23	74.1 ± 11.8	
Chronic Disease								
Present	18	5	51.80	10.34	31.54	72,07	73.1 ± 14.1	0.372
Absent	16	3	97.03	11.85	73.80	120.26	78.7 ± 11.0	
Tumor Size								
≤ 5 cm	12	2	98.44	13.23	72.50	124.38	90.0 ± 9.5	0.186
> 5 cm	22	6	51.49	10.93	30.07	72.91	67.9 ± 12.7	
FIGO Stage								
Early (I - II)	29	6	85.06	11.88	61.77	108.34	80.0 ± 9.3	0.089
Advanced (III - IV)	5	2	18.13	3.63	11.03	25.24	53.3 ± 24.8	
Histologic Type								
Leiomyosarcoma	10	3	55.51	12.84	30.34	80.68	75.0 ± 15.8	
MMMT	10	2	41.71	10.40	31.34	62.09	57.1 ± 24.9	0.939
ESS	5	1	51.20	8.77	34.02	68.38	80.0 ± 17.9	
Others	9	2	88.96	17.91	53.87	124.06	88.9 ± 10.5	
Histologic Grade								
Low	7	1	103.71	15.08	74.16	133.27	85.7 ± 13.2	0.114
Moderate	8	0	No statistics are computed because all cases are censored					
High	18	7	38.35	8.04	22.59	54.12	58.1 ± 15.2	
Myometrial Invasion								
Absent	7	2	44.29	9.46	25.75	62.83	62.5 ± 21.3	
< 50%	12	4	65.94	18.45	29.78	102.10	77.9 ± 14.1	0.691
≥ 50%	10	1	89.50	14.15	61.77	117.23	83.3 ± 15.2	
Lenfovascular Involvement								
Present	13	5	56.97	14.86	27.84	86.10	83.6 ± 10.8	0.062
Absent	18	3	93.57	13.28	67.55	119.60	65.8 ± 14.1	
Lenf Nodes Status								
Positive	1	1	12.00	0.00	12.00	12.00	0.0 ± 0.0	**0.048**
Negative	18	4	76.32	12.40	52.02	100.63	68.1 ± 14.0	
Residual Tumor								
Present	3	2	8.00	0.94	6.15	9.85	33.3 ± 27.2	**<0.001**
Absent	21	4	54.4	7.53	39.65	69.15	72.7 ± 14.1	
Adjuvant Therapy								
Yes	19	5	67.97	13.13	42.25	93.69	72.2 ± 12.2	0.553
No	15	3	85.78	16.51	53.42	118.14	79.1 ± 13.8	

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Recurrence								
Present	14	7	36.29	9.73	17.22	55.36	52.1 ± 16.4	**0.004**
Absent	20	1	113.67	6.16	101.60	125.73	94.4 ± 5.4	
Site of Recurrence								
Pelvic Peritoneum	6	4	30.40	10.01	10.79	50.01	53.3 ± 24.8	
Lung	3	1	60.00	19.60	21.59	98.41	66.7 ± 27.2	0.688
Others	5	2	19.73	3.41	13.05	26.42	53.3 ± 24.8	
ki-67								
Positive	16	5	57.28	9.20	39.26	75.31	71.4 ± 12.2	0.424
Negative	18	3	88.44	15.78	57.52	119.36	82.0 ± 12.2	

FIGO,International Fenderation of Obstetrics and Gynecology; MMMT, malignant mixed mullerian tumor; ESS, endometrial stromal sarcoma

Table 4. Cox Regression Analysis Results for Disease Free Survival Times (Months)

	Hazard Ratio	%95 Confidence Interval		p
		Lower	Upper	
Age	0.995	0.891	1.112	0.935
Age at Menarche	2.273	1.056	4.890	**0.036**
Age at First Delivery	1.989	1.168	3.386	**0.011**
Parity	2.283	0.598	8.715	0.227
Tumor Size	1.572	1.132	2.184	**0.007**

Table 5. Cox Regression Analysis Results for Survival Times (Months)

	Hazard Ratio	%95 Confidence Interval		p
		Lower	Upper	
Age	1.103	0.966	1.260	0.146
Age at Menarche	2.095	0.841	5.221	0.112
Age at First Delivery	1.469	0.951	2.268	0.083
Tumor Size	1.459	0.888	2.396	0.136

Uncorrected Proof

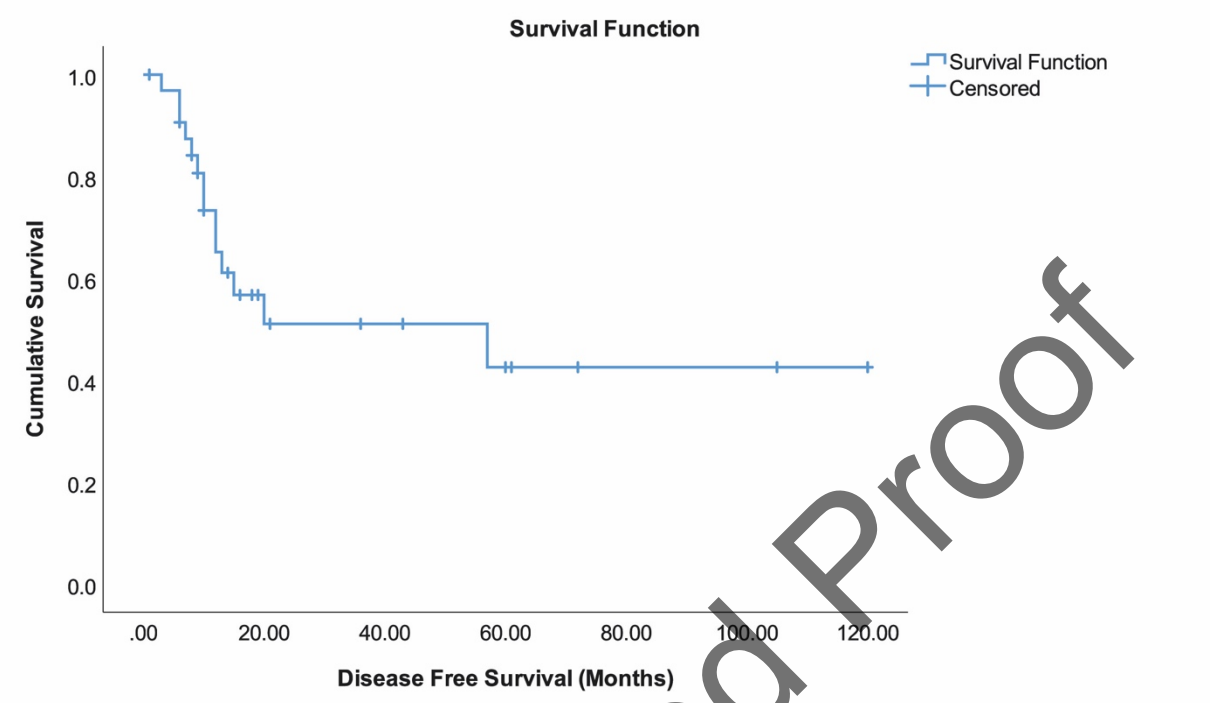

Figure 1. Disease-free survival times of patients

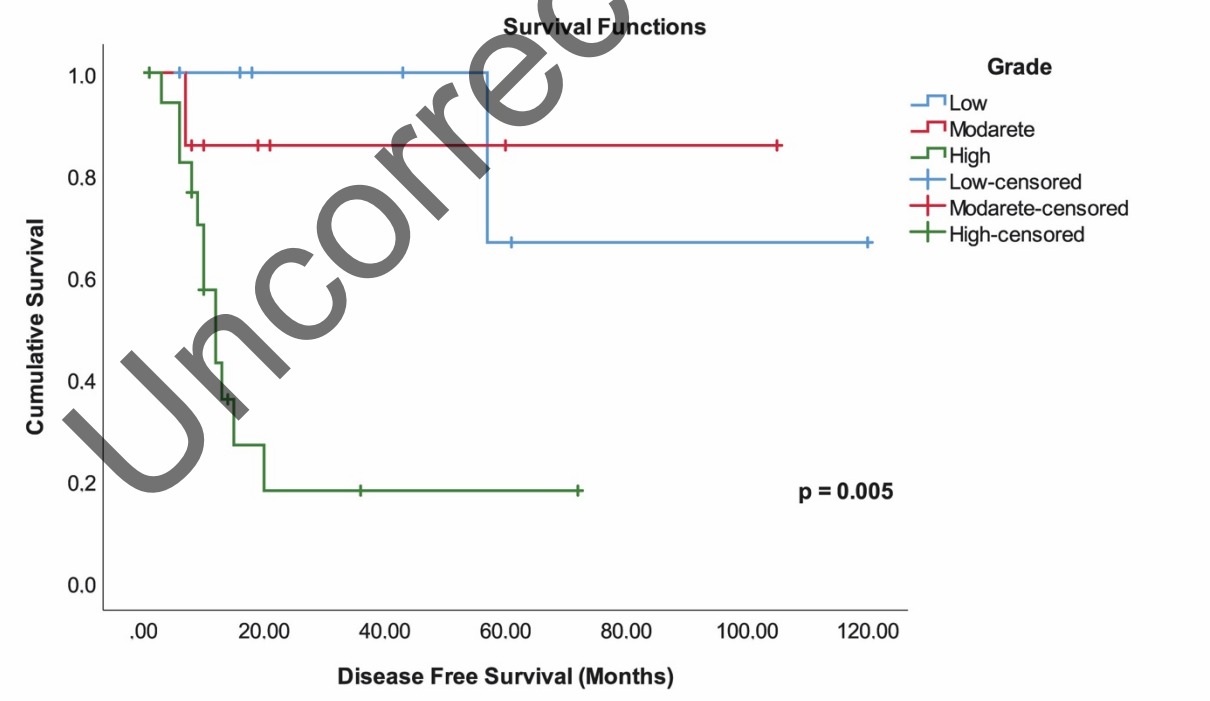

Figure 2. Disease-free survival times by tumor grade

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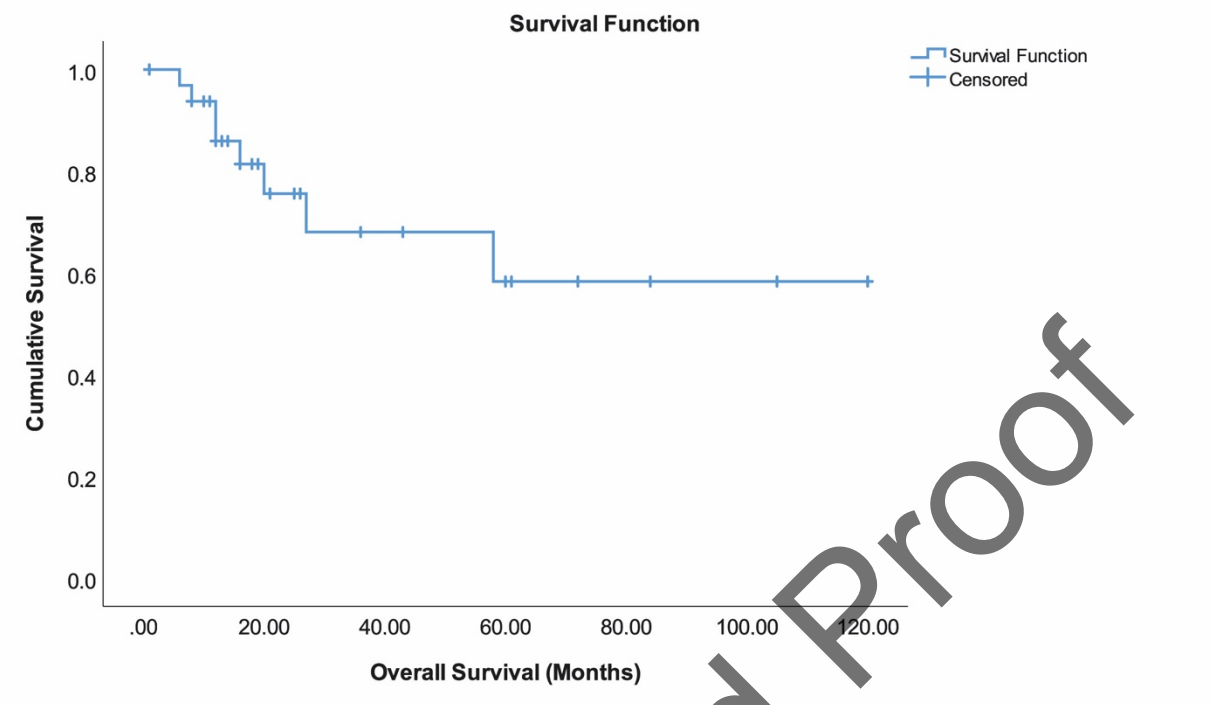

Figure 3. Overall survival times of patients

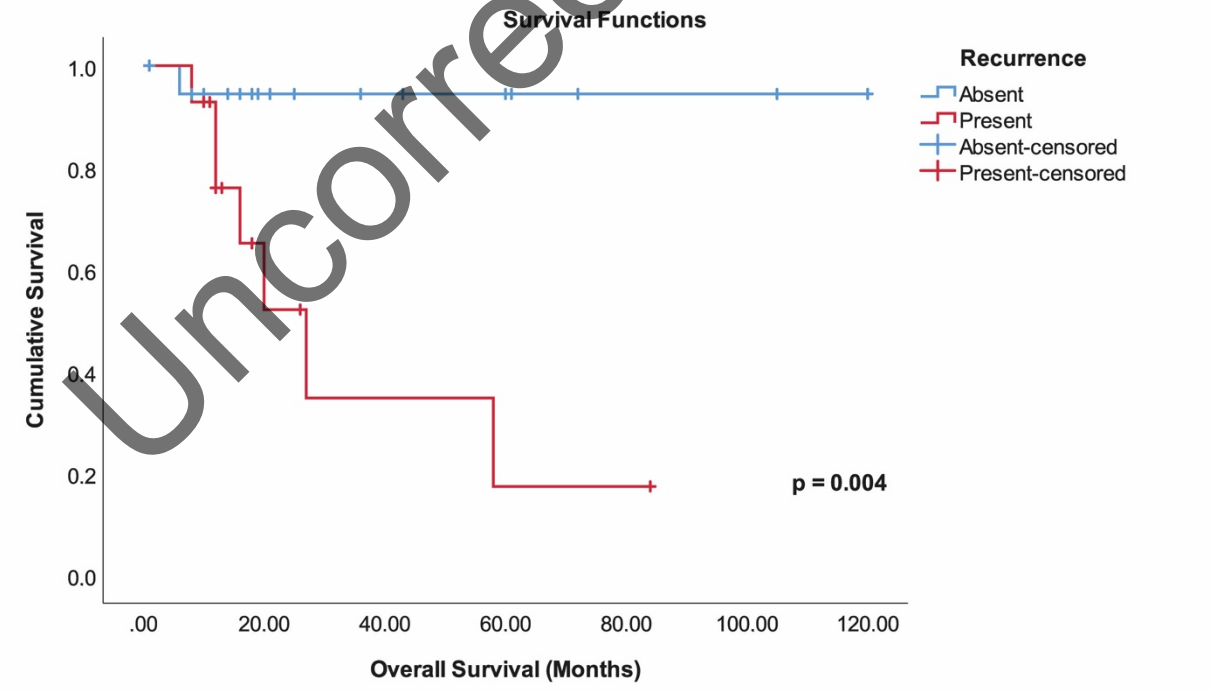

Figure 4. Overall survival times by recurrence

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