ORIGINAL RESEARCH

Clinicopathological Profile, Surgical Practices and Outcomes of the Patients with Uterine Sarcoma: A Single Institutional Study from Eastern India

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Abstract

Aim: The study aimed to analyze the clinicopathological profile, surgical practices, and survival outcomes of the patients with uterine sarcoma in eastern India.

Background: Uterine sarcomas are a rare entity among gynecological malignancies with a very unfavorable prognosis. Due to its rarity, there is no consensus on a standardized treatment approach.

Materials and methods: A retrospective analysis of all patients with a histopathological diagnosis of uterine sarcomas who were treated in our institute from 2012 to 2016 was done. The clinical parameters, treatment given, histopathological report, stage, and follow-up details of all patients were reviewed. Survival analysis was done using Kaplan–Meier method.

Results: From 2012 to 2016, 40 patients with a diagnosis of uterine sarcoma were recorded. The median age of the patients was 44 years (range, 18–68 years). The youngest patient who got treated was an 18-year-old with low-grade endometrial stromal sarcoma (LGESS) with stage IIIC disease. Majority of the patients presented with abnormal uterine bleeding (60%) followed by abdominal pain (30%). Low-grade endometrial stromal sarcoma (42%) was the most frequent histological subtype of uterine sarcoma encountered followed by leiomyosarcoma (LMS) (40%), adenosarcoma (AS) (7.5%), undifferentiated endometrial sarcoma (UES) (5%), high-grade endometrial stromal sarcoma (HGESS) (2.5%), and uterine smooth muscle tumor of uncertain malignant potential (STUMP) (2.5%). Majority of the patients were diagnosed at stage I (92.5%) and only 2.5% of patients had stage IIIC disease. The patients were followed up for a median duration of 15 (range, 4–180) months. The median survivals of the patients diagnosed with different histological subtypes were 32, 11, 4, 9.5, 26, and 42 months for LGESS, LMS, HGESS, UES, AS, and STUMP, respectively. Median disease-free survival (DFS) for the entire cohort of uterine sarcoma was 32 months, and median overall survival (OS) was 57 months.

Conclusion: Uterine sarcoma, when diagnosed even at an early stage was associated with increased recurrence rate and mortality.

Clinical significance: Due to its aggressive behavior, an early diagnosis and a multimodal treatment approach should be considered.

Keywords: Adenosarcoma, Endometrial stromal sarcoma, Fertility sparing surgery, Leiomyosarcoma, Ovarian preservation, Uterine sarcoma, Uterine smooth muscle tumors of uncertain malignant potential.

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Introduction

Uterine sarcomas are a heterogeneous group of tumors of mesenchymal origin and they account for approximately 3–7% of all uterine malignancies.[1] According to the World Health Organization (WHO), 2014 classification,[2] uterine sarcomas are classified into LMS, endometrial stromal sarcoma (ESS), and AS. Endometrial stromal sarcomas are further classified into the following three main types: (i) LGESS, (ii) HGESS, (iii) UES.[3] Uterine sarcomas with histologic features (nuclear atypia, necrosis, or mitosis) that are not fulfilling the criteria of LMS fall into the category of uterine STUMP.[3] After the exclusion of carcinosarcoma from the classification of uterine sarcomas, LMS has become the most common histological subtype and is associated with a poor prognosis. AS except those with sarcomatous overgrowth and LGESS have a favorable prognosis,[4,5] but HGESS and UES are highly malignant tumors with poor survival and high recurrence rate.[6] Radiation exposure, and the long-term use of tamoxifen or estrogen analogs are considered to be the risk factors.[7,8] The stage of the disease is considered to be an important prognostic factor.[9] Even when diagnosed at an early stage, the 2-years survival rate is reported less than 50%.[10] Elderly age group, black race, size of the tumor, and the presence of extrauterine metastasis at the time of diagnosis were the factors affecting the survival.[11] Due to its rarity and diversity in the histological types, the common consensus on risk factors associated with poor outcomes and standard treatment is not available. The aim of the study is to analyze the clinicopathological profile, surgical practices, and survival outcomes of patients diagnosed with uterine sarcoma.

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Materials and Methods

The clinical data of the patients who had undergone treatment for uterine sarcoma at Acharya Harihar Postgraduate Institute of Cancer from January 2012 to December 2016 were retrospectively analyzed. The clinical parameters, histopathological report, imaging details, treatment details, recurrence pattern, and follow-up details were recorded. The International Federation of Gynecology and Obstetrics (FIGO) 2009 staging for uterine sarcoma, which includes two divisions, one for LMS and ESS and one for AS, was used to stage the patients. The upfront surgery was performed in all patients which included hysterectomy with or without ovarian preservation and excision of extra-uterine disease. The decision regarding adjuvant treatment was based on multi-disciplinary tumor board discussion and varied on case-to-case basis. The patients were followed-up every 3 months for the first 2 years and every 6 months for the next 3 years. All patients were followed until December 2021 and the patients who missed a schedule were contacted telephonically.

Statistical Analysis

Statistical analysis of the data was done with IBM SPSS Statistics, Version 23.0 (Armonk, NY: IBM). To describe the categorical variables, descriptive statistics such as frequency analysis and percentage analysis were used. Chi-squared test was used to identify the significance of categorical variable. The continuous variables were expressed in mean, median, and standard deviation. Kaplan–Meier curve was plotted to analyze the survival outcome. A *p*-value of <0.05 considered statistically significant.

Results

From 2012 to 2016, 40 patients with diagnosis of uterine sarcoma were treated in our institute. The median age at presentation was 44 (range 18–68) years. The youngest patient who got treated was an 18-year-old with LGESS of stage IIIC disease. Majority of the patients presented with abnormal uterine bleeding (60%) followed by abdominal pain (30%). LGESS (42%) was the most frequent histological type followed by LMS (40%), AS (7.5%), UES (5%), HGESS (2.5%), and STUMP (2.5%). Majority of the patients were diagnosed at stage I (92.5%) and only 2.5% of patients were diagnosed at stage IIIC disease. The demographic, clinical, and pathological features are summarized in Table 1. Surgical resection was the upfront treatment given in all patients. Surgery included total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO) and resection of extra-uterine disease. A total of four patients had a vaginal hysterectomy as they had preoperative investigations suggestive of uterine fibroid. One patient underwent hysteroscopic-guided polypectomy and had LMS confined to the polyp. The patient had two live births following the resection of the polyp and she was free of the disease on her last follow-up. An adjuvant treatment in the form of radiotherapy was administered in three patients and as chemotherapy in six patients. The radiation dose delivered was 50 Gray in 25 fractions and the chemotherapy regimen administered was Ifosfamide and doxorubicin. The presence of residual disease, extra-uterine metastasis, and recurrence were the factors considered for adjuvant treatment. Table 2 shows the details of the patients who had a recurrence. The entire cohort of the patients were followed-up for an average duration 15 (range, 4–180) months. The median survivals of the patients diagnosed with different histological types were 32, 11, 4, 9.5, 26, and 42 months for LGESS, LMS, HGESS, UES, AS, and STUMP respectively. Median DFS for the entire cohort of uterine sarcoma was 32 months, and median OS was 57 months (Fig. 1).

Discussion

Uterine sarcomas are highly aggressive malignancy with a dismal prognosis. A case series of 11 patients with the diagnosis of uterine sarcoma reported a median survival of 6.5, 18, and 56 months for LMS, ESS, and AS, respectively, with a 5-years OS of only 20%.[12] Similar outcomes were reported in a retrospective study on 61 patients with a median OS of 31.07 months, but their cohort

Table 1: Clinical characteristics of the patients with uterine sarcoma

Parameters	*LMS*	*LGESS*	*HGESS*	*UES*	*AS*	*STUMP*
No. of patients	16	17	1	2	3	1
Median age at presentation (in years)	47.5 (26–68)	40 (18–66)	46	48 (46–50)	41 (34–60)	46
Clinical presentations						
Abdominal pain	7	2	0	1	1	1
Bleeding P/V	8	13	1	1	2	0
Primary infertility	1	2	0	0	0	0
Stage						
IA	1 (6.2)	4 (23.5)	0	1	0	0
IB	14 (87.5)	12 (70.6)	1	1	2 (66.7)	1
IIA	1 (6.2)	0	0	0	0	0
IIIB	0	0	0	0	1	0
IIIC	0	1	0	0	0	0
Median OS (in months)	11 (1–84)	32 (1–120)	4	9.5	26 (6–180)	42

AS, adenosarcoma; HGESS, high-grade endometrial stromal sarcoma; LGESS, low-grade endometrial stromal sarcoma; LMS, leiomyosarcoma; UES, undifferentiated stromal sarcoma; STUMP, stromal tumor of unknown malignant potential

Table 2: Details of the patients who had recurrence of the disease

Age (years)	*Surgery*	*HPR*	*Stage*	*Adjuvant treatment*	*Site of recurrence*	*DFS (months)*	*OS (months)*	*Status*
30	TAH BSO	LGESS	IB	No	Lungs	6	48	Dead
46	TAH BSO omentectomy resection of deposit over mesocolon	HGESS	IB	No	Pelvis	3	4	Dead
68	TAH BSO	LMS	IB	No	Pelvis	12	18	Dead
18	TAH BSO BPLND	LGESS	IIIC1	Chemotherapy	Bowel deposit	6	12	Dead
50	TAH BSO	LMS	IB	No	Vaginal vault and parietal wall	4	8	Dead
60	TAH BSO omentectomy	AS	IB	No	Pelvis	120	180	Dead
65	TAH BSO	LMS	IB	No	Lungs	16	18	Dead

BPLND, bilateral pelvic lymphadenectomy; BSO, bilateral salpingo-oophorectomy; HPR, histopathology; TAH, total abdominal hysterectomy

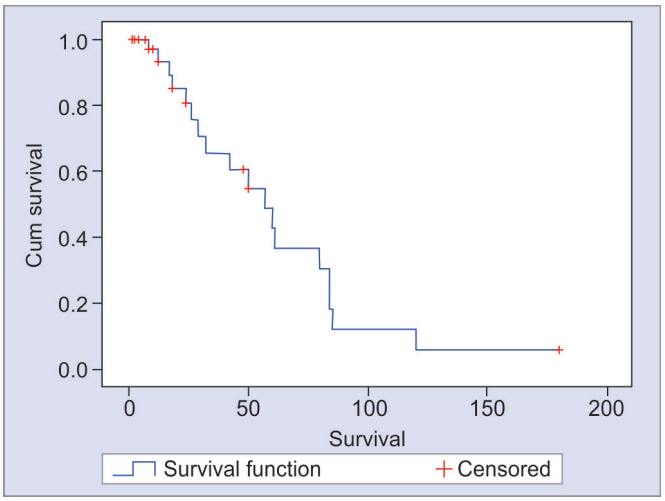

Fig. 1: Kaplan–Meier curve showing the survival of patients with uterine sarcoma. The *x*-axis represents the time in months, *y*-axis the cumulative survival

included patients with Ewings sarcoma and rhabdomyosarcoma in addition to LMS, HGESS, and UES.[13] Longest survival was reported for ESS and shortest for carcinosarcoma in a retrospective study on 42 patients.[11] Older age, advanced stage, presence of necrosis, and high mitotic index increased the hazard ratio of mortality.[11] From the results of our study, the median survival of patients with LGESS, LMS, HGESS, UES, AS, and STUMP were 32, 11, 4, 9.5, 26, and 42 months, respectively, and the median DFS for the entire cohort of uterine sarcoma was 32 months, and the median OS was 57 months. The better survival in this study may be attributed to the following reasons: Patients diagnosed with carcinosarcoma were excluded, most of the patients were managed in early stages, and LGESS was the most common histological type encountered which naturally had a better prognosis when compared to other histological subtypes. The patient with HGESS had the worst prognosis and STUMP had the best prognosis. Despite adjuvant chemotherapy, stage IIIC patients had a poor prognosis with DFS of only 4 months. The patients who did not receive any adjuvant treatment were the ones who died of recurrence. Although uterine sarcomas are considered to be a disease of elderly population,[10] 45% of the patients were less than 40 years of age in this study. Older age group has been reported as one of the poor prognostic factors in the literature,[14] similar to our study.

Several studies in the literature have reported LMS as the most common histological subtype of uterine sarcoma.[15,16] In contrary, LGESS was the most frequent type followed by LMS in this study. These differences could be due to the demographics of different populations, a small number of patients, and changes in WHO classification in each study.

Total abdominal hysterectomy and removal of the extra-uterine disease is the primary treatment for uterine sarcoma.[17] The role of pelvic and para-aortic lymphadenectomy in uterine sarcoma is unclear. Based on a retrospective analysis of 52 patients, it was observed systematic pelvic and para-aortic lymphadenectomy improved the survival.[18] However, the incidence of nodal metastasis in patients with LMS was only 3.5–7%[1,19] and 70% of these patients also had distant metastasis proving no prognostic effect at any stage.[20] While some studies favor systematic pelvic and para-aortic lymph node dissection, others recommend removal of only enlarged and suspicious nodes in patients with ESS.[21] In this study, lymphadenectomy was done in seven patients, but nodal metastasis was found in only one patient who ultimately developed recurrence within a period of 6 months from the date of surgery. In line with the previously quoted studies, our study demonstrated no survival benefit in patients who had undergone lymphadenectomy.

Since a significant number of patients with uterine sarcomas were diagnosed in the premenopausal period, ovarian preservation should be considered in these patients. It is considered to be safe in LMS and AS, as the risk of ovarian involvement is very low and did not affect the survival.[4,22–24] However, in cases of LGESS, the role of ovarian preservation is questioned as these tumors express hormonal receptors.[25–27] In a retrospective analysis of 53 patients with stage I ESS by Li N et al, there was an increased rate of recurrence observed in the patients who had undergone ovarian preservation.[28] Yoon et al. reported no survival benefits in patients who had undergone BSO.[26] In our study, 26 patients had undergone BSO and 15 patients underwent ovarian preservation. There was no ovarian metastasis identified in the oophorectomy specimens and ovary was not the site of recurrence in the cases where ovaries were preserved. Hence, ovaries should be preserved when diagnosed in premenopausal age; at the same time, the risk-benefit ratio should be explained especially in case of LGESS.

Kapp et al., reported a poor OS in the fertility-preserving treatment arm (43%) when compared to the standard treatment arm (73%).[19] In this study, one patient had a polypectomy and the histopathology report was LMS confined to the polyp. In the absence of any specific guidelines regarding fertility-preserving treatment, it is difficult to come to any conclusion.

Surveillance, epidemiology, and end result (SEER) database analysis of 13,089 patients demonstrated improved survival in patients who received adjuvant radiotherapy,[10] similar to that noticed in this study. However, other studies reported no survival benefit with any form of adjuvant treatment in recent decades.[29,30] Large prospective trials are needed to analyze the role of radiotherapy and chemotherapy in uterine sarcoma.

In this study, the adjuvant treatment was decided based on the presence of extra-uterine metastasis, residual disease, and recurrence. Seven patients developed recurrence, six of them received no adjuvant treatment initially as the disease was localized to the uterus. Early-stage at diagnosis and upfront surgery with complete resection were considered to be good prognostic factors.[31] The low survival rates observed in all types of uterine sarcoma may reflect a rapid progression of the disease and the limited treatment options available.

Conclusion

To conclude, the patient with the diagnosis of HGESS had the worst OS and the patients with STUMP and LGESS had better survival. Despite 40% of patients in the reproductive age group, the median OS was 57 months indicating aggressive behavior of the disease. This study had few limitations including small sample size with lesser number of patients in each histological subtype, retrospective in nature, and the adjuvant treatment varied between the cases which makes it difficult to generalize the result. Randomized prospective control trials are needed to study more precisely the risk factor associated with poor prognosis and to formulate the standard treatment.

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