

# Fertility sparing in uterine sarcomas: single center experience of 13 patients

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## Summary

**Purpose of Investigation:** The feasibility and safety of conservative surgery is not well defined for fertility sparing approach for uterine sarcoma due to very low incidence and poor prognosis. The authors present their experience regarding fertility preservation for uterine sarcoma. **Materials and Methods:** A total of 13 patients with uterine sarcoma were included in this retrospective case study; endometrial stromal sarcoma (ESS) (n=6) and leiomyosarcoma (LMS) (n=7). Patients data, including clinicopathological characteristics and prognostic information were extracted from medical records. Excision of mass and reconstruction of uterus was performed for fertility sparing in all patients and staging surgery (bilateral pelvic and para-aortic lymphadenectomy ± omentectomy) as performed for five cases (one ESS case and four LMS cases). **Results:** The median size of the mass was 8.5 (range: 1-22) cm. Median follow-up time was 54 (range 13-142) months. Recurrence rate was 69.2% (9/13). The mean relapse interval was 30.69 months. Four patients died and all of them was diagnosed with LMS. Four pregnancies (37%) were recorded. Two of them occurred with assisted reproductive technologies (intracytoplasmic sperm injection), the other two pregnancies were spontaneous, and all of them had a cesarean delivery. **Conclusion:** Patients should be informed about prognosis of uterine sarcomas and risk of fertility preserving approach. Close follow-up is obligatory and complementary surgery should be performed after completion of fertility due to high recurrence rate and poor prognosis especially with LMS.

**Key words:** Fertility preservation; Uterine sarcomas; Leiomyosarcoma; Endometrial stromal sarcoma (ESS).

## Introduction

Uterine sarcomas are rare malign mesenchymal tumors which originate from myometrial smooth muscle or supportive connective tissue of uterus; representing approximately 3-8% of all uterine malignancies and 1% of all genital malignancies [1, 2]. They are a heterogeneous group of tumors from both pathological and clinical perspectives, are classified according to the type of the cells which they developed [3], and also behavior of these tumors are heterogeneous and depend on stage and grade of disease. The most common type is leiomyosarcoma (LMS) that is an aggressive tumor with poor prognosis (five-year survival rate: 18.8-68%). Although ESS is associated with better prognosis than LMS and undifferentiated endometrial sarcomas (UES), it has a late recurrence rate (14-60%), and UES has a very aggressive tumoral behavior (five year survival rate: 25-55%). Adenosarcomas are very rare tumors and have better prognosis than others (five-year survival rate > 80%) [4].

Incidence of uterine sarcomas is very low and are usually seen in over 40-year-old women after completing fertility [5]. Therefore the standard primary treatment, hysterectomy with/without salpingo-oophorectomy, is per-

formed for these tumors. However these tumors are rarely seen in reproductive age and in these patient groups, psychological problems are seen due to psychosocial pressure of cancer associated fertility problem, hence fertility preservation is important in these patient groups. There is furthermore no consensus regarding feasibility and safety of fertility preserving management in these patient group due to low incidence rate and the heterogeneity of previously published series.

In the present study, the authors focused on uterine sarcoma which is seen at reproductive age women with fertility desire that were treated at the present center. The authors' experience in fertility sparing surgery for uterine sarcoma and a review of related literature are also discussed.

## Materials and Methods

The authors analyzed 13 consecutive patients with uterine sarcoma, undergoing fertility sparing surgery between January 2004 and December 2016, from a retrospective database in the present tertiary center. The ethics committee of the hospital was approved for the study. In this series, excision of mass with negative tumor border and reconstruction of uterus was performed for fertility

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Table 1. — *Clinical characteristics and outcomes of patients with uterine sarcoma.*

	ESS	LMS
Patients (n)	6	7
Age (median)	31.5	28
Marital status	3 married	7 married
Prior pregnancy (n)	1	2
Stage	6 IB	1 IA 6 IB
Adjuvant treatment	2 megestrol 1 paclitaxel + carboplatin	3 IMA
Recurrence rate (%)	66.7	71.4
PFS (mean-months)	29.278	38.857
Death rate	0	57.1
Pregnancy outcome	1 pregnancy No live birth 1 ICSI	3 pregnancies 3 live births 1 ICSI 2 spontaneous

ICSI: intracytoplasmic sperm injection

sparing in all patients and staging surgery (bilateral pelvic and para-aortic lymphadenectomy ± omentectomy) was performed for five cases (one ESS case and four LMS) depending on the patient's parity status, age, the extent of disease, and their informed consent. Surgical procedures for patients who were included in the study were performed by one gynecologic oncology surgeon (A.A.) and histopathological examination of the tumors were performed according to the 2014 WHO Classification by two different pathologist with comprehensive back-up in gyno-oncological pathology. Before the fertility sparing surgery, all patients were efficiently informed about the high risk of recurrence and the fertility of patients were assessed with anti-Müllerian hormone level and antral follicular count. After the fertility sparing surgery, patients were followed-up with clinical history, physical examination, transvaginal ultrasonography every three months in the first year, and then every six months. Abdominal scan with computed tomography or magnetic resonance imaging and chest X-rays were planned every six months for the first two years and then performed yearly. Patient data, including demographic and clinicopathological characteristics and prognostic information were extracted from the medical records. Descriptive and frequency analyses were performed by using SPSS version 22.0.

Table 2. — *Descriptives of the patients.*

	Age (year)	Gravida/parity	Diagnosis/Grade/Stage	Surgical procedure	Adjuvant treatment	Recurrence	Follow up (months)	PFS (months)	OS (months)	Pregnancy outcome	Status
Case 1	30	1/0	Low grade ESS Stage IB	Excision of mass	-	-	13	13	13	ICSI No live birth	Alive
Case 2	29	-	Low grade ESS Stage IB	Excision of mass	Megesterol acetate	+	41	14	41	-	Alive
Case 3	32	-	Low grade ESS Stage IB	Excision of mass + staging surgery	Megesterol acetate	+	56	7	56	-	Alive
Case 4	35	1/1	Low grade ESS Stage IB	Excision of mass	Paclitaxel + carboplatin	+	67	6	67	-	Alive
Case 5	32	-	Low grade ESS Stage IB	Excision of mass	-	-	73	73	73	-	Alive
Case 6	26	0	Low grade ESS Stage IB	Excision of mass	-	+	142	54	142	-	Alive
Case 7	24	0	LMS Stage IB	Excision of mass	-	+	31	10	31	-	Exitus
Case 8	32	2/2	LMS Stage IB	Excision of mass	IMA	+	16	9	16	Spontaneous Live birth	Exitus
Case 9	28	1/1	LMS Stage IA	Excision of mass + staging surgery	-	-	74	74	74	Spontaneous Live birth	Alive
Case 10	37	0	LMS Stage IB	Excision of mass + staging surgery	-	-	85	85	85	-	Alive
Case 11	23	0	LMS Stage IB	Excision of mass + staging surgery	IMA	+	28	9	28	-	Exitus
Case 12	27	3/3	LMS Stage IB	Excision of mass	-	+	109	70	109	ICSI Live birth	Alive
Case 13	32	0	LMS Stage IB	Excision of mass + staging surgery	IMA.	+	29	11	29	-	Exitus

ICSI: intracytoplasmic sperm injection, LMS: leiomyosarcoma, ESS: endometrial stromal sarcoma, IMA: ifosfamide and nimustine.

## Results

Six cases were diagnosed with ESS and seven cases were diagnosed with LMS. Median age at diagnosis was 29.5 (range 23-37) years. Nine patients were nulliparous, two patients had one child, one patient had two children, and one of them had three children (Table 1). Eight patients had abnormal uterine bleeding, three had abdominal pain, and two enlargement of abdomen. The median size of the mass was 8.5 cm, ranging between 1 and 22 cm. Lymph node dissection was performed in six (40%) cases according to the stage of disease. The mean number of removed lymph nodes was 45.14 per patient (range: 8–69). There were no metastatic lymph nodes. Adjuvant therapy was administered in six cases, hormonal therapy (megesterol acetate) in two ESS (15.4%) cases, and chemotherapy in four (three LMS and one ESS) (30.8%) cases. Therefore, seven (53.8%) cases did not receive any adjuvant therapy (Table 2).

Median follow-up time for ESS was 61.5 months, ranging between 13 and 142 months and for LMS it was 31 months, ranging between 16 and 109 months. The mean relapse interval for ESS was 29.278 months and for LMS it was 38.857 months. Recurrence rate for ESS was 66.7% (4/6) and for LMS it was 71.4% (5/7). Three patients that had recurrences were limited to uterus and full staging procedure was performed for each patient. One patient who had recurrence limited to uterus had undergone complementary surgery with ovarian preservation, but after 92 months, she had recurrence with multiple abdominal implants and debulking surgery was performed. In five LMS patients, recurrences occurred and full staging surgery was performed for three patients; one of them died without secondary surgery. One patient had vulvar epithelioid leiomyosarcoma after local wide excision and unilateral inguino-femoral lymph node dissection with 15 mm tumor free borders and lymph nodes. After six months, patient presented with groin metastasis and a six-week pregnancy. She had a very strong fertility desire. During her second trimester she received three cycles of iphosphamide plus adriamycin chemotherapy and delivered a 28-week live newborn infant with caesarian section. During caesarian section, uterine and ovarian metastasis were explored and hysterectomy was performed. After three months, she died due to radiation-resistant cranial and spinal metastases.

Four patients died and all of them were diagnosed with LMS. Four pregnancies (37%) were recorded. Two of them occurred with assisted reproductive technologies (intracytoplasmic sperm injection) and the other two pregnancies were spontaneous, and all of them had a caesarian delivery.

## Discussion

Uterine sarcomas are very rare neoplasms that have interested gynecologic oncologists and pathologists for years. These tumors generally present with abnormal vaginal bleeding, pain, and enlargement of abdominal mass, as presented in the patients in this study. Grade, stage, and cell type of these tumors which are dependent on pathologic diagnosis, are important for classification, prognosis, and treatment procedures [6]. Generally the first line therapy for uterine sarcoma is a radical surgery but these tumors sometimes affect women during their reproductive age and children, and these patients group desire a conservative surgery for fertility sparing. Therefore in the literature there is very limited data regarding fertility sparing therapy for uterine sarcomas due to the very low incidence of these tumors and larger case series and studies are needed to improve treatment protocols [7-10]. In this study, the present authors reported their uterine sarcoma series which were treated with fertility sparing therapies: six ESS cases and seven LMS cases.

LMS is a very rare malignancy and accounts for approximately 1% of all uterine malignancies, 70% of all are uterine sarcomas. It is very aggressive tumor of the uterus and mostly responsible for uterine cancer related deaths [11]. So surgical procedure such as total abdominal hysterectomy with/without bilateral salpingo-oophorectomy (BSO) is usually performed after diagnosis of LMS. Therefore in both advanced and early stage LMS, effective treatments are difficult due to aggressive behaviour of tumor and resistance to adjuvant therapy such as chemotherapy or radiotherapy and high recurrence rate (local or distant) (approximately 70%) even in radical surgery and five-year survival rate in Stage I 76%, in Stage II 60%, in Stage III 45%, in Stage IV 29%, and independent of stage 40% [12, 13]. Although it is usually seen in the postmenopausal period (median age is 56 years) [14], it can also be seen during the reproductive age, and in these patient groups fertility preservation is very important because of psychosocial pressure. Management of these patient is controversial because the experience with fertility sparing treatment in LMS is limited. In the literature there are few case series reporting fertility sparing treatment of LMS. In a case series of nine cases published in 1982, hysterectomy was performed in three cases and only myomectomy was performed in the remaining six patients. Recurrence was observed in only one case and the other five cases were alive without recurrence four years after myomectomy and pregnancy was obtained in three cases [15]. Davids *et al.* were performed myomectomy to 1,150 patients and five of them diagnosed with LMS. Any additional treatment were not been performed to these patients and pregnancy was obtained in three cases [16]. Lissoni *et al.* reported eight cases with fertility sparing surgery for LMS. In this case series, the mean mitotic count of LMS was 6 per 10 HPF (5

Table 3. — Brief review of the literature of ESS.

Study	Patients (n)	Age (median)	Pregnancy outcome	Follow-up (months) (median)	Grade	Adjuvant treatment	Recurrence rate (%)	Death rate	PFS (months)
Lissoni <i>et al.</i> , 1997 [23]	6	27	2 pregnancies 1 livebirth 2 spontaneous	51	5 low-grade 1 high-grade	-	0	0	nr
Stadsvold <i>et al.</i> , 2005 [24]	1	16	nr	21	1 low-grade	Megestrol	0	0	nr
Koskas <i>et al.</i> , 2009 [25]	1	34	1 pregnancy 1 livebirth 1 ICSI	Not reported	1 low-grade	-	100	-	10
Yan <i>et al.</i> , 2010 [21]	1	25	1	40	1 low grade	Etoposide – cisplatin	0	0	nr
Delaney <i>et al.</i> , 2012 [26]	1	16	1	108	-	Megestrol	0	0	nr
Sanchez-Ferrer <i>et al.</i> , 2012 [27]	1	32	1 ICSI	60	1 low grade	Megestrol	1	0	31
Bai <i>et al.</i> , 2014 [7]	19	nr	8 pregnancies 5 livebirth	nr	nr	nr	nr	nr	nr
Dong <i>et al.</i> , 2014 [28]	1	25	1 pregnancy 1 livebirth	31	1 low grade	Medroxy- progesterone acetate	0	0	nr
Choi <i>et al.</i> , 2014 [8]	1	31	1 pregnancy 2 livebirths 1 IVF	99	1 low-grade	Letrozole	0	0	nr
Morimoto <i>et al.</i> , 2015 [29]	1	25	nr	120	nr	Medroxy- progesterone acetate	1	1	12
Noventa <i>et al.</i> , 2015 [30]	1	34	1 pregnancy	19	1 low-grade	nr	0	0	nr
Zhan <i>et al.</i> , 2014 [31]	1	26	1 pregnancy 1 livebirths	47	1 low-grade	Medroxy- progesterone acetate	0	0	nr
Jin <i>et al.</i> , 2015 [32]	5	28-36 (range)	3 pregnancies 3 livebirths 1 ICSI	21-55	nr	Megesterol acetate or triptrelin	1 (20%)	0	Three months for one case. The other four cases are nr.
Laurelli <i>et al.</i> , 2015 [33]	6	18-40 (range)	3 pregnancies 2 livebirths	30-70	1 low-grade	Megesterol acetate (5 case)	0	0	nr
Xie <i>et al.</i> , 2017 [34]	17	15-37 (range)	5 pregnancies 5 livebirths	39	1 low-grade	Medroxypro- gesterone ace- tate (5 cases) Megesterol acetate (5 cases) GnRHa (2 cases) GnRHa + LNG-IUD (2 cases)	10 (58.8%)	0	17.9 (range 3-52)
Present case series	6	31.5	1 pregnancy No livebirth 1 ICSI	61.5	6 low-grade	2 megestrol 1 paclitaxel + carboplatin	83.3	0	21.83 (range 6-54)

n: number, nr: not reported, ICSI: intracytoplasmic sperm injection, IVF: in-vitro fertilization, GnRHa: Gonadotropin releasing hormone analogue, IUD: intrauterine device

to 33). Pregnancy was obtained in three cases and two of them had a spontaneous delivery at term. In the last case recurrence was observed at cesarian section. In spite of radical surgery additional chemotherapy, she died [10]. In the present case series, seven cases were diagnosed as LMS and median mitotic count was 11 per 10 HPF, ranging between 4 to 30. Three pregnancies were recorded. One of them occurred with assisted reproductive technologies (intracytoplasmic sperm injection), the other two pregnancies were spontaneous, and all of them had a caesarian delivery. Myomectomy was performed in all patients. Recurrence was observed in five cases (71.4%) and four of them died (57.1%). The present authors believe that treatment of LMS in infertile patients is very complicated. Patients and relatives should be informed about prognosis of LMS and risk of fertility sparing treatment. The final decision must be left to them after being well informed. Close follow-up is obligatory after conservative treatment and radical surgical procedure should be completed after successful pregnancy due to high recurrence rate and aggressive tumor behaviour. However information should be given that the patient may die after pregnancy and a child's growth without mother should be assessed from a sociological perspective.

ESS represent approximately 15% of all uterine sarcomas (second most common uterine sarcoma after LMS) [17]. ESS have been divided into four different types; low-grade ESS (LG-ESS), high-grade ESS (HG-ESS), endometrial stromal nodule (ESN), and undifferentiated uterine sarcoma (UUS) according to clinicopathologic, immunohistochemical, and molecular features [17]. Total abdominal hysterectomy plus BSO with/without pelvic lymphadenectomy is the standard treatment of ESS (recently a minimal invasive surgery is discussed) [18]. The ESS survival rate is extremely good in contrast of LMS, with about 89% of patients living at least ten years after being diagnosed with Stage I disease and 66% in Stage IV disease [19]. Recurrence of LG-ESS is very rare: 16-43% at patients with BSO and 68-100% of patients without BSO, and the median relapse time is 65 months. The reason for high recurrence rate in patients without BSO is that ESS is an estrogen-dependent tumor [20]. In the literature there are rare case reports or series of successful pregnancies after fertility sparing surgery and a brief review of the literature and the present clinical outcomes is shown in Table 3 for ESS, respectively [7, 8, 21, 23-34]. In the present case series, six cases were diagnosed as ESS and excision of mass was performed in all patients because of desiring fertility of these patients. All of these patients had a LG-ESS but recurrence was observed in four cases (66.7%) and the mean relapse interval was 29.278 months. There was a high recurrence rate due to ovarian preservation in the present cases. Complementary treatment was performed in these patient and they are all alive and healthy. One pregnancy was recorded from these patients and this pregnancy oc-

curred with assisted reproductive technologies (intracytoplasmic sperm injection), but resulted in abortion. However successful pregnancy could not be achieved in the present case series and high recurrence rate after conservative surgery; the present authors believe that only excision of mass for fertility preservation is a good choice in meticulously selected and highly motivated patients with LG-ESS due to evidence in the literature for good prognosis of LG-ESS after conservative surgery. However patients should be followed closely in gynecologic oncology centers for high risk of recurrence and the radical surgical procedure should be performed after completion of fertility.

In conclusion, in recent years fertility sparing treatment procedures for cancer patients in reproductive ages have increased and might be an applicable alternative to radical surgery. However fertility sparing procedure for uterine sarcoma patients is still controversial because of poor prognosis and high recurrence rate of these tumors. Even so these patients with uterine sarcoma may choose fertility sparing surgery due to psychosocial pressure of cancer associated fertility problem. So patients and relatives should be informed about prognosis of uterine sarcomas and risk of fertility preserving approach. Determination of treatment procedure must be left to them after being well informed and if patients choose conservative treatment, they should be followed closely after conservative treatment and complementary surgery should be performed after successful pregnancy, due to high recurrence rate and poor prognosis especially with LMS.

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