

Unexpected uterine sarcomas after hysterectomy and myomectomy for presumed leiomyoma: a retrospective study of 26,643 patients

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Hanyu Cao^{1,*}
Lin Li^{1,*}
Bowen Yang²
Gupo Luo²
Jiangyan Lou¹
Mingrong Xi^{1,*}

¹Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University, Chengdu City, Sichuan Province, People's Republic of China; ²Key Laboratory of Birth Defects and Related Diseases of Women and Children, West China Second Hospital, Sichuan University, Chengdu City, Sichuan Province, People's Republic of China

*These authors contributed equally to this work

Objectives: We conducted this study to explore the clinical characteristics, prognosis, and prevalence of unexpected uterine sarcoma (UUS) after hysterectomy and myomectomy for presumed leiomyoma.

Study design: The records of women who underwent hysterectomy or myomectomy through laparoscopy or laparotomy for preoperatively presumed uterine leiomyomas from January 2009 to December 2016 were reviewed and data were retrospectively analyzed.

Results: Eleven patients had morcellation of uterine sarcoma. Eighty-eight patients were diagnosed with uterine sarcomas (total prevalence: 0.33%) including 29 leiomyosarcomas (LMS), 48 endometrial stromal sarcomas (ESS), and 11 adenosarcomas. ESS patients with advanced stage were significantly associated with worse overall survival ($p < 0.01$).

Conclusion: Only 0.33% of patients who underwent surgery for presumed leiomyoma experienced UUS, and advanced stage seemed to be the single prognostic factor for sarcoma. However, the time interval between initial treatment and secondary definitive surgery was not shown to impact prognosis. In addition, the small number of UUS patients having morcellation (4 LMS and 7 ESS) may be underpowered to detect differences in survival.

Keywords: adenosarcomas, endometrial stromal sarcomas, leiomyosarcomas, morcellation, prognosis

Introduction

Uterine leiomyomas or fibroids are benign neoplasms that arise from smooth muscles of the uterus, with an incidence of nearly 70% in white women by age 50 and >80% for black women.¹ As the most common indication for hysterectomy in the United States, leiomyomas impose a heavy burden on health care costs annually.² The majority of patients are asymptomatic, while up to 40% report symptoms such as prolonged menstruation or menorrhagia, abdominal pain, urinary complaints, and even infertility.³ Transvaginal ultrasound serves as the most cost-effective adjuvant method to diagnose a pelvic mass, providing both high sensitivity and specificity. Nevertheless, it may still be difficult to distinguish between myomas and malignant sarcomas preoperatively as they resemble each other in appearance. Uterine sarcomas are a rare heterogeneous group, originating from the smooth muscle or mesenchyme of the uterus comprising leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), adenosarcoma, undifferentiated sarcoma, and other rare subtypes. Surgical resection remains the gold standard for uterine sarcomas, including total abdominal hysterectomy with or without bilateral salpingo-oophorectomy, while the role of

Correspondence: Mingrong Xi
Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University, 17 Renmin South Road, Chengdu City, Sichuan Province, People's Republic of China
Tel +86 1 818 060 9008
E-mail xmrjzz@126.com

lymphadenectomy remains controversial.⁴ The prevalence of uterine sarcomas found incidentally during or after surgery for presumed myomas varies from 0% to 0.6%.^{5–8} Overall survival (OS) rates are reported to be <50% even in early stages.⁹ Prognosis is especially poor in LMS, in which the tumor size has been reported as a major prognostic indicator.^{10–12} Owing to the nonspecific symptoms and histologic variety, there is no evidence-based consensus regarding prognostic factors and optimal management.¹³

The present study was conducted to provide a retrospective analysis of unexpected uterine sarcoma (UUS) during an 8-year period while analyzing clinicopathologic features and identifying the prognostic value of previously proposed indicators. In addition, we explore whether the timing of reoperation plays an important role in the prognosis of uterine sarcomas.

Materials and methods

This study was approved by the Ethics Committee of West China Second University Hospital, a tertiary hospital in Southwest China, and was carried out following the principles of the Helsinki Declaration. Informed consent was waived due to the retrospective of the study which involves only data analysis of existing medical records, patients' privacy was not breached and the patient's informed consent is not required. The records of uterine sarcoma patients who underwent surgical treatment for presumed leiomyoma from March 2009 to December 2016 were retrospectively reviewed. All cases of incidentally discovered LMS, ESS, and adenosarcomas were included. The diagnosis of uterine sarcoma was confirmed by gynecologic pathologists in West China Second University Hospital at the time of surgery. A tumor is diagnosed as LMS rather than smooth muscle tumor of uncertain malignant potential STUMP if it had either: 1) geographic necrosis; 2i) ≥ 10 mitoses per 10 high-power fields plus diffuse or multifocal atypia (moderate–severe). Relevant information was extracted including age at diagnosis, gravidity, parity,

menopausal state, body mass index (BMI), chief complaint, tumor size, stage, type of initial surgery (hysterectomy or myomectomy), method of initial surgery (laparoscopy or laparotomy), morcellation, secondary surgery, lymphadenectomy, lymph node metastasis, lymphovascular invasion, and adjuvant treatment (chemotherapy and radiotherapy). Staging was based on the International Federation of Gynecology and Obstetrics 2009 classification system. For patients who had undergone secondary surgery, the time interval between first and second surgery was included in the analysis and separated into two groups (≤ 30 days, >30 days).

OS was defined as the period from diagnosis to either the day of death or last visit. All statistical tests were performed using SPSS software version 18.0 (SPSS, Inc, Chicago, IL, USA). Survival analyses were performed with Kaplan–Meier survival curves, and a Cox proportional hazards model was used to assess the prognostic variables of interest. A two-tailed probability value of <0.05 on univariate analysis was considered statistically significant and was used for inclusion in the multivariate analyses. Proportional hazards assumption test has been done by using time-dependent covariates.

Results

Incidence of UUS and LMS

During the 8-year period, 26,643 patients underwent hysterectomy or myomectomy by laparoscopy or laparotomy for preoperatively presumed uterine leiomyomas in our hospital. A total of 88 patients were diagnosed with UUS, pathologically confirmed during or after surgery, with the total prevalence of UUS being 0.33% and the prevalence of LMS being 0.11%. Among these, 4183 patients underwent laparoscopic hysterectomy, 7133 underwent total abdominal hysterectomy, 6902 had laparoscopic myomectomy, and 8425 had abdominal myomectomy. The incidence of these four groups is presented in Table 1.

Table 1 Incidence of unexpected uterine sarcoma found at hysterectomy or myomectomy

	Hysterectomy		Myomectomy		Total number
	Laparoscopy	Laparotomy	Laparoscopy	Laparotomy	
UUS, n	11	47	13	17	88
LMS, n	4	16	4	5	29
Total, n	4183	7133	6902	8425	26,643
Rate of UUS (%)	0.26	0.66	0.19	0.20	0.33
Rate of LMS (%)	0.10	0.22	0.60	0.60	0.11

Abbreviations: LMS, leiomyosarcomas; UUS, unexpected uterine sarcomas.

Clinicopathologic features

Patient characteristics are shown in Table 2. Forty-eight (54.6%) patients were diagnosed with ESS, including 45 low-grade and 3 high-grade ESS. Twenty-nine (33%) patients had LMS, and the remaining 11 (12.5%) patients had adenosarcomas. The median age of all included patients at diagnosis was 45 (range 17–78) years. Patients with adenosarcomas were older than patients in the other groups. Gravidity and parity ranged from 0 to 8 and 0 to 6 in LMS and ESS, respectively. Forty-eight percent of patients were premenopausal and 52% were perimenopausal/postmenopausal. Patients with LMS had the highest median BMI of 24.56 (16.19–31.18) kg/m². Prolonged menstruation or menorrhagia was the most common primary complaint for all three groups, followed by palpable mass. The largest tumor size >5 cm was found in 18 (81.81%) LMS, 22 (51.16%) ESS, and 4 (50%) adenosarcoma patients, respectively. Most LMS patients (96.6%) were diagnosed at stage I compared with ESS (83.3%) and adenosarcoma (90.9%). For their first surgery, 69% of LMS, 58.3% of ESS, and 90.9% of adenosarcoma patients underwent hysterectomy rather than myomectomy while 72.4% of LMS, 75% of ESS, and 63.6% of adenosarcoma underwent laparotomy instead of laparoscopy. A total of 11 (12.5%) patients had morcellation during surgery including 4 LMS and 7 ESS patients. In 66 (75%) patients who underwent reoperation, 39 (59.1%) had their secondary surgery within 30 days. Among 62 (70.5%) patients who underwent lymphadenectomy including removal of pelvic and/or para-aortic lymph nodes, only 4 patients with ESS were found to have lymph node metastasis. Moreover, the rate of lymphovascular space invasion was 17.2% in LMS, 27.1% in ESS, and 9.1% in adenosarcoma patients. A total of 37 (42.1%) patients did not receive any additional treatment, while 41 (46.6%) had chemotherapy, and 10 (11.4%) received both chemotherapy and radiotherapy.

Prognostic factors and outcomes

Median follow-up for all 88 UUS patients was 60 (range: 13–102) months. For each specific subtype, median follow-up was 48 (range: 13–100) months for LMS, 61 (range: 15–102) months for ESS, and 68 (range: 15–102) months for adenosarcomas, respectively. Relapses occurred in 21 patients, including 10 LMS, 6 ESS, and 5 adenosarcomas. Twenty patients died of their diseases including 9 LMS, 6 ESS, and 5 adenosarcomas. The unadjusted 5-year cumulative OS rates for the three

histologic subtypes were compared separately using log-rank test, and the corresponding Kaplan–Meier curves are shown in Figure 1. ESS patients had a favorable OS rate of 87.2% (95% CI: 77.6–96.8%) compared with patients with LMS (OS: 65.3%, 95% CI: 45.1–85.5%) and adenosarcoma (OS: 59.7%, 95% CI: 28.5–90.9%). Log-rank test showed that there were no significant differences among the three groups only for OS ($p = 0.06$). For the univariate analysis, stage II–IV ESS patients showed a significantly poorer OS rate compared with stage I patients (95% vs 50%, $p < 0.01$; Figure 2). The results of multivariate analysis also revealed stage to be the unique prognostic factor for ESS patients. However, other indicators, including age, gravidity, parity, menopausal status, BMI, chief complaints, surgical procedure, lymphovascular space invasion, lymph node metastasis, or adjuvant treatment did not show a significant impact on survival.

Discussion

Uterine sarcomas are rare and aggressive tumors accounting for <5% of all uterine malignancies.¹³ Previously, they were classified as carcinosarcomas (40%), LMS (40%), ESS (15%), undifferentiated sarcoma (5–10%), and adenosarcomas (5%).^{14,15} The International Federation of Gynecology and Obstetrics reclassified carcinosarcoma as an undifferentiated carcinoma of the endometrium in 2009 because of recent evidence regarding molecular and genetic origins, though others claimed that it displayed a higher rate of extrauterine spreading and recurrence than endometrial carcinoma.^{16,17} As a result, carcinosarcoma was excluded from the present study.

In the current study, ESS was the main subtype, similar to the results of Zhang et al and Gao et al in a Chinese population.^{18,19} In the current study, 66 UUS patients underwent hysterectomy or myomectomy initially and then a second surgery, 17 of them were upstaged, Cusido et al and Lee et al demonstrated no difference in survival of patients undergoing hysterectomy or myomectomy as their initial surgery.^{20,21} Morcellation was demonstrated to be an independent prognostic indicator in previous studies by increasing intraperitoneal spreading.^{22,23} However, in the current study, the small number of UUS patients having morcellation (4 LMS and 7 ESS) may be underpowered to detect differences in survival. Lymphadenectomy was performed in 68.9% of UUS patients in the current study, whereas revealing no survival benefit in UUS. In addition, according to a study

Table 2 Characteristics of patients diagnosed with unexpected uterine sarcoma

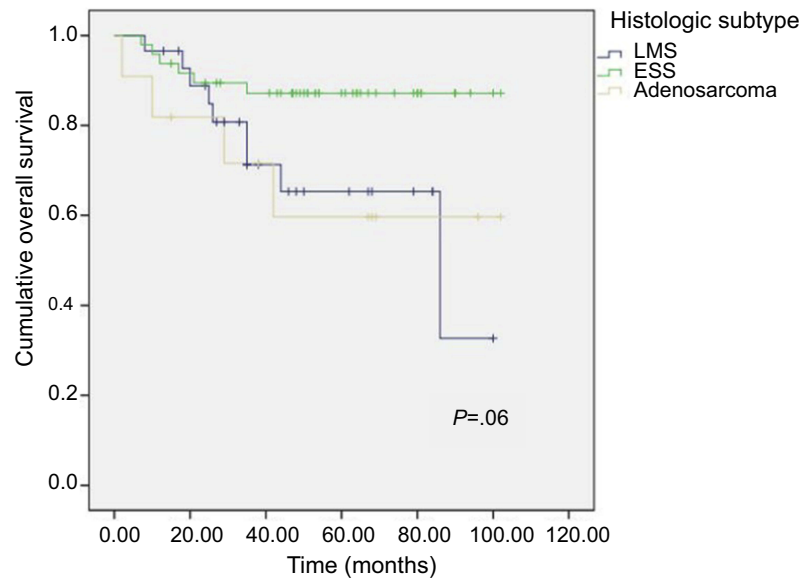
Characteristic	Total (n=88)	LMS (n=29)	ESS (n=48)	Adenosarcoma (n=11)
Median age, years (range)	45 (17–78)	44 (31–68)	43 (17–66)	48 (30–78)
Median gravidity (range)	3 (0–8)	3 (0–8)	3 (0–6)	2 (0–5)
Median parity (range)	1 (0–6)	1 (0–6)	1 (0–6)	1 (0–2)
Menopausal status, n				
Premenopause, n	42	15	22	5
Perimenopause/postmenopause, n	46	14	26	6
Body mass index, kg/m ²	23.18 (16.02–31.18)	24.56 (16.19–31.18)	22.83 (16.02–29.38)	21.01 (16.23–30.43)
≤23	41	13	22	6
>23	44	15	24	5
Primary complaints				
Asymptomatic, n	12	6	4	2
Pelvic pain, n	13	5	7	1
Prolonged menstruation or menorrhagia, n	31	9	18	4
Palpable mass, n	21	7	12	2
Other complaints, n	11	2	7	2
Stage				
I, n	78	28	40	10
II–IV, n	10	1	8	1
First surgery				
Hysterectomy, n	58	20	28	10
Myomectomy, n	30	9	20	1
Laparoscopy, n	24	8	12	4
Laparotomy, n	64	21	36	7
Morcellation				
Yes, n	11	4	7	0
No, n	77	25	41	11
Second surgery				
Yes, n	66	24	37	5
Time interval ≤30, n	39	15	22	2
Time interval >30, n	27	9	15	3
No, n	22	5	11	6
Lymphadenectomy				
Yes, n	61	25	30	6
No, n	27	4	18	5
Lymph node metastasis				
Positive, n	4	0	4	0
Negative, n	57	25	26	6
Lymphovascular space invasion				
Yes, n	19	5	13	1
No, n	69	24	35	10
Adjuvant therapy				
No, n	37	12	22	3

(Continued)

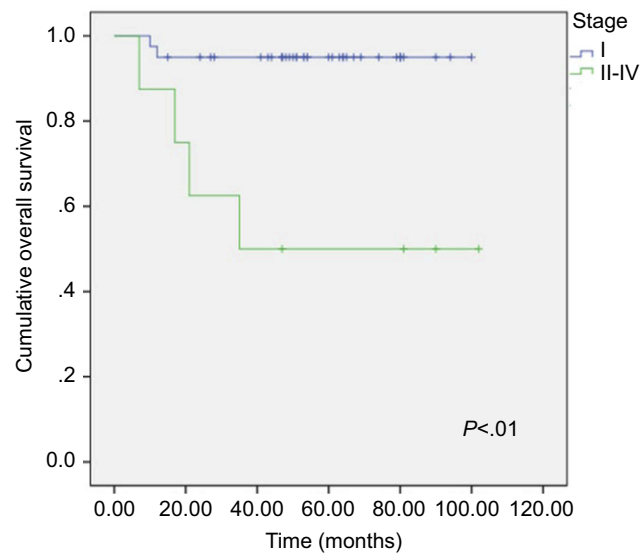
Table 2 (Continued).

Characteristic	Total (n=88)	LMS (n=29)	ESS (n=48)	Adenosarcoma (n=11)
Chemotherapy, n	41	13	21	7
Chemotherapy+radiotherapy, n	10	4	5	1

Abbreviations: ESS, endometrial stromal sarcoma; LMS, leiomyosarcomas.

**Figure 1** Overall survival curves for three subtypes.

Abbreviations: ESS, endometrial stromal sarcoma; LMS, leiomyosarcomas.

**Figure 2** Overall survival curves for stages of endometrial stromal sarcoma in univariate analysis.

based on the National Cancer Database, the largest analysis of women with LMS, not performing lymphadenectomy did not negatively impact survival.¹² Previous studies have explored the risk of UUS for different age groups and reported that age was an independent prognostic factor for OS of uterine sarcomas.¹⁸ However, the current study did not find any significant association between age and survival of occult uterine sarcomas. Also in the current study, BMI ranged from 16.02 to 31.18 kg/m² but did not reveal a significant association between BMI and OS, while a previous cross-sectional study by Lin et al demonstrated a significant association

between elevated BMI and poor quality of life.²⁴ Being in perimenopause or after menopause was highest in the ESS group. Fibroids occur more frequently with increased exposure to estrogen.²⁵ Therefore, women after menopause planning surgery for presumed benign leiomyoma found in clinical practice should especially beware. However, the state of menopause was not found to be associated independently with survival in UUS in the current study, which differs from the results of Gao et al.¹⁹ Although tumor size was found to have important prognostic value in previous studies, we failed to find its predictive value of prognosis even in LMS.

Table 3 Recent studies reporting the prevalence of unexpected uterine sarcomas

First author	Year	Country	Patients, N	Primary diagnosis	Intervention	Total sarcoma, n	Leiomyosarcoma, n
Lieng ²⁵	2014	Norway	4791	Leiomyoma	Hysterectomy or myomectomy ± morcellation	20 (0.42%)	20 (0.42%)
Mahnert ²⁶	2015	USA	1325	Leiomyoma ± abnormal uterine bleeding	Hysterectomy	5 (0.38%)	ND
Zhao ⁷	2015	People's Republic of China	10,248	Leiomyoma	Hysterectomy or myomectomy ± morcellation	48 (0.47%)	13 (0.13%)
Paul ⁶	2016	India	2075	Leiomyoma	Myomectomy ± morcellation	6 (0.29%)	2 (0.10%)
Zhang ¹⁵	2016	People's Republic of China	3021	Leiomyoma	Hysterectomy ± morcellation	18 (0.60%)	5 (0.17%)
Lee ¹⁷	2016	Korea	ND	Leiomyoma	Hysterectomy or myomectomy ± morcellation	45	18
Kho ²⁷	2016	USA	10,119	Leiomyoma	Hysterectomy ± morcellation	9 (0.09%)	5 (0.05%)
Raine-Bennett ²⁸	2016	USA	34,728	Leiomyoma	Hysterectomy ± morcellation	125 (0.36%)	81 (0.23%)
Ruengkachorn ²⁹	2017	Thailand	11,258	Leiomyoma	Hysterectomy	22 (0.20%)	19 (0.17%)
Pavlakakis ³⁰	2017	Greece	631	Leiomyoma	Hysterectomy or myomectomy ± morcellation	8 (1.27%)	5 (0.79%)
Damasco ²⁴	2017	Australia	1878	Leiomyoma	Hysterectomy ± morcellation	5 (0.27%)	0 (0.0%)
Current study	2018	People's Republic of China	26,643	Leiomyoma	Hysterectomy or myomectomy ± morcellation	88 (0.33%)	29 (0.11%)

Abbreviation: ND, no data.

Stage was found to be the unique prognostic factor in the current study in accordance with previous evidence.^{18,19} Moreover, the time interval between initial treatment (including neoadjuvant radiation or surgery) and secondary definitive surgery has been shown to impact outcomes of patients with gallbladder cancer.²⁶ Possible explanations include the lack of a proper recovery period for subsequent tumor evaluation and pathologic diagnosis or lack of clear visualization through imaging examination after inflammation; this may be significant for management guidelines and follow-up surveillance.²⁶ However, in the current study, a significant association between time interval and survival in UUS was not found.

In 2014, the US Food and Drug Administration announced a rate of 1 in 352 cases for UUS based on data from nine studies between 1990 and 2012.²⁷ The most recent studies reporting the prevalence of UUS in surgery for presumed leiomyomas are noted in Table 3 and were published between 2012 and 2017.^{6,7,18,20,28–35} The maximum number of patients was 34,728, and incidence of UUS ranged from 0% to 0.79%. The current study population is the largest in recent years, and estimates of UUS and LMS found incidentally in patients undergoing hysterectomy and myomectomy were 0.33% and 0.11%, respectively.

There are several limitations in the current study that should be taken into consideration. First, the non-randomized, retrospective nature may limit standards for diagnosis and evaluation. Second, conducted in a university-based tertiary hospital, this study included many referral patients with more severe clinical presentations, including older age or larger palpable mass and may not be representative of the whole population and lead to selection bias. In addition, the follow-up time may appear to be insufficient. Third, owing to the small number of patients in the survival analysis, clinical significance of the prognostic factors should be accepted with caution. Moreover, our data were from a single center and the combined analysis of different histologic sarcoma types with different biological behavior in our study may decrease statistical power to demonstrate differences in prognosis.

Conclusion

Only 0.33% of patients who underwent surgery for presumed leiomyoma experienced UUS in the current study. ESS was the main subtype of UUS, and advanced stage appeared to be the adversely impact the prognosis of ESS. Further multicenter, prospective clinical trials are warranted to substantiate these findings.

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Disclosure

The authors report no conflicts of interest in this work.

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