Clinicopathological Characteristics and Prognosis of Uterine Sarcoma: A 10-Year Retrospective Single-Center Study in China

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Abstract

Purpose: Uterine sarcoma is a rare and heterogeneous gynecological malignancy characterized by aggressive progression and poor prognosis. The current study aimed to investigate the relationship between clinicopathological characteristics and the prognosis of uterine sarcoma in Chinese patients.

Patients and Methods: In this single-center retrospective study, we reviewed the medical records of 75 patients with histologically verified uterine sarcoma treated at the First Affiliated Hospital of Xi'an Jiaotong University between 2011 and 2020. Information on clinical characteristics, treatments, pathology and survival was collected.

Progression-Free Survival (PFS) and Overall Survival (OS) were visualized in Kaplan-Meier curves. Prognostic factors were identified using the log-rank test for univariate analysis and Cox-proportional hazards regression models for multivariate analysis.

Results: The histopathological types included 36 Endometrial Stromal Sarcomas (ESS, 48%), 33 Leiomyosarcoma (LMS, 44%) and 6 adenosarcomas (8%). The mean age at diagnosis was 50.2 ± 10.7 years. Stage I and low-grade accounted for the majority. There were 26 recurrences and 25 deaths at the last follow-up. The mean PFS and OS were 89.41 (95% CI: 76.07-102.75) and 94.03 (95% CI: 81.67-106.38) months, respectively. Univariate analysis showed that >50 years, post-menopause, advanced stage, ≥ 1/2 myometrial invasion, lymphovascular space invasion and high grade were associated with shorter survival (P<0.05). Color Doppler flow imaging positive signals were associated with shorter PFS in the LMS group (P=0.046). The ESS group had longer PFS than that of the LMS group (99.56 *vs.* 76.05 months, P=0.043). The multivariate analysis showed that post-menopause and advanced stage was independent risk factors of both PFS and OS in the total cohort and LMS group. In the ESS group, diagnosis age >50 years and high-grade were independent risk factors of PFS, while high-grade and lymphovascular space invasion were independent risk factors of OS.

Conclusion: In Chinese patients with uterine sarcoma, post-menopause and advanced stage were associated with a significantly poorer prognosis. The prognosis of ESS was better than that of LMS. Color Doppler flow imaging positive signals of the tumor helped to identify LMS, which needs to be further tested in a larger sample in the future.

Keywords: Uterine sarcoma, Clinicopathological characteristics; Prognosis; Survival; Chinese patients

Abbreviations

PFS: Progression-Free Survival; OS: Overall Survival; CS: Carcinosarcoma; ESS: Endometrial Stromal Sarcomas; LMS: Leiomyosarcomas; UUS: Undifferentiated Sarcoma; LG-ESS: Low-Grade ESS; HG-ESS: High-Grade ESS; FIGO: International Federation of Gynecology and Obstetrics; CA125: Cancer Antigen 125; TH-BSO: Total Hysterectomy with Bilateral Salpingo-Oophorectomy; CDFI: Color Doppler Flow Imaging; LVSI: Lymphovascular Space Invasion; SD: Standard Deviations; PT: Paclitaxel and Platinum; IAP: Ifosfamide + Epirubicin + Cisplatin; CI: Confidence Interval

Introduction

Uterine sarcoma is a rare and aggressive heterogeneous malignant tumor originating from the mesodermal tissues (muscle and supportive tissues) [1]. It is characterized by nonspecific clinical presentations, high recurrence rates and poor prognosis, accounting for about 1% of female genital tract malignancies and 3% to 7% of uterine cancers [2]. The incidence of uterine sarcoma increases with age and is reported to be about 6.4 per 100,000 in women aged above 50 years in America [3].

According, to the traditional histological classification, uterine sarcoma mainly Included Carcinosarcoma (CS), Leiomyosarcoma (LMS), Endometrial Stromal Sarcoma (ESS), Undifferentiated Sarcoma (UUS) and other less frequent histological subtypes, such as adenosarcoma. In 2009, the International Federation of Gynecology and Obstetrics (FIGO) revised the staging system and reclassified CS as endometrial cancer due to its similar dedifferentiated or metaplastic form to endometrial cancer [2]. The new uterine sarcoma classification mainly contains three pathological subtypes: LMS, ESS and adenosarcoma, of which LMS is the most common [4].

Diagnosis of uterine sarcoma is generally difficult before surgery because of nonspecific symptoms, such as irregular vaginal bleeding, abdominal or pelvic mass and pain, or even no symptom [4,5]. Ultrasonography, magnetic resonance imaging, computed tomography and Cancer Antigen 125 (CA125) level are useful preoperative diagnostic methods. However, distinguishing uterine sarcoma from benign uterine lesions such as fibroids is difficult due to the lacking specific symptoms or diagnostic techniques, resulting in high misdiagnosis rates, which may lead to serious consequences [6,7].

There is no standardized treatment for uterine sarcoma due to its rarity and heterogeneity. Early-stage uterine sarcoma is mainly treated by surgery according to different pathological types, including Total Hysterectomy with Bilateral Salpingo-Oophorectomy (TH-BSO) [8]. For advanced-stage uterine sarcoma, complete cytoreduction is embraced as the most effective therapy [8]. The effects of lymphadenectomy and adjuvant treatments remain inconclusive, contributing to the dilemma in managing the disease. The reported 5-year survival rate was 45% to 50% for stage I-II and decreased to 0% to 15% for advanced stages [9]. Importantly, there are suggestions that the efficiency of treatments can be different among racial populations, indicating the need for therapeutic-tailored strategies [10].

The present study aimed to evaluate the relationship between the prognostic factors, such as clinicopathological characteristics, surgical practices, adjuvant therapies and survival with uterine sarcoma at our institution. The objectives of our evaluation were to increase understanding and individualize the treatment of the disease, to review the data for potential guidelines for therapeutic decisions, and to compare survival outcomes with the different prognostic factors in this rare group of heterogeneous malignancies.

Materials and Methods

Case inclusion

This study utilized a retrospective design to evaluate patients with histologically verified uterine sarcoma, who were diagnosed and treated at the Department of Gynecology and Obstetrics of the First Affiliated Hospital of Xi'an Jiaotong University from January 2011 to December 2020. The inclusion criteria included: (1) pathologically confirmed uterine sarcoma; (2) complete clinical, pathological and follow-up information. The exclusion criteria included: (1) other cancers excluding breast cancer; (2) metastatic or other sites' sarcomas; (3) endometrial carcinosarcoma; (4) currently pregnant; (5) histories of preoperative chemotherapy or radiotherapy; (6) lost to follow-up. Finally, a total of 75 cases were included in this study. The requirement for written informed consent from participants was waived due to the retrospective nature of the study. Verbal informed consent was obtained from surviving patients and the family members of deceased patients during phone call follow-up. They were approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2023LSK-275).

Data extraction

The following clinical data were extracted from medical records: Age at diagnosis, menopausal status, early symptoms, FIGO stage, initial diagnosis, tumor size, Color Doppler Flow Imaging (CDFI), CA125 level, surgery type and time, lymph node metastasis, adjuvant therapy, histological type, histological grade (low grade indicates high differentiation, while high grade indicates low differentiation), myometrial invasion (<1/2, ≥ 1/2), and Lymphovascular Space Invasion (LVSI). The surgical staging was defined by the FIGO 2009 staging system.

Outcome measures

Survival information was acquired by telephone and medical records. Progression-Free Survival (PFS) was defined from the first time for surgery to that of disease progression or recurrence. Overall Survival (OS) was defined as the time from initial surgery to death from all causes [11]. The analysis cut-off date was set at July 5th, 2022, with survival times calculated in months.

Statistical analysis

Categorical variables were presented as frequencies (percentages), and continuous variables as means ± Standard Deviations (SD), or medians and ranges. Prognostic factors for PFS and OS were examined by the log-rank tests for univariate analysis. Significant factors in univariate analysis and clinically significant indicators were included in the Cox regression model for further multivariate analysis. Survival curves were plotted using the Kaplan-Meier method. Differences among curves were analyzed by the log-rank tests. $P<0.05$ was considered as statistically significant. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Results

General information of patients

Over the 10-year study period, a total of 335 uterine sarcoma cases were confirmed and retrieved from the Department of Gynecology and Obstetrics of the First Affiliated Hospital of Xi'an Jiaotong University. Following stringent adherence to our inclusion and exclusion criteria, 75 cases were enrolled ultimately, including ESS (n=36), LMS (n=33) and adenosarcoma (n=6). Detailed process of case inclusion was shown in Figure 1. The median follow-up period was 50 months (range: 4.7-132.3 months).

Table 1 showed the general information of patients. The mean age at diagnosis was 50.2 ± 10.7 years old (range: 31-81 years), which served as the threshold to categorize patients into two groups. Forty-nine (65.3%) patients were premenopausal and 26 (34.7%) were post-menopausal. A tumor size of over 5 cm was a prerequisite for surgery and was used as a critical point in this study. The most frequent

Figure 1: Flow chart of the patient selection process.
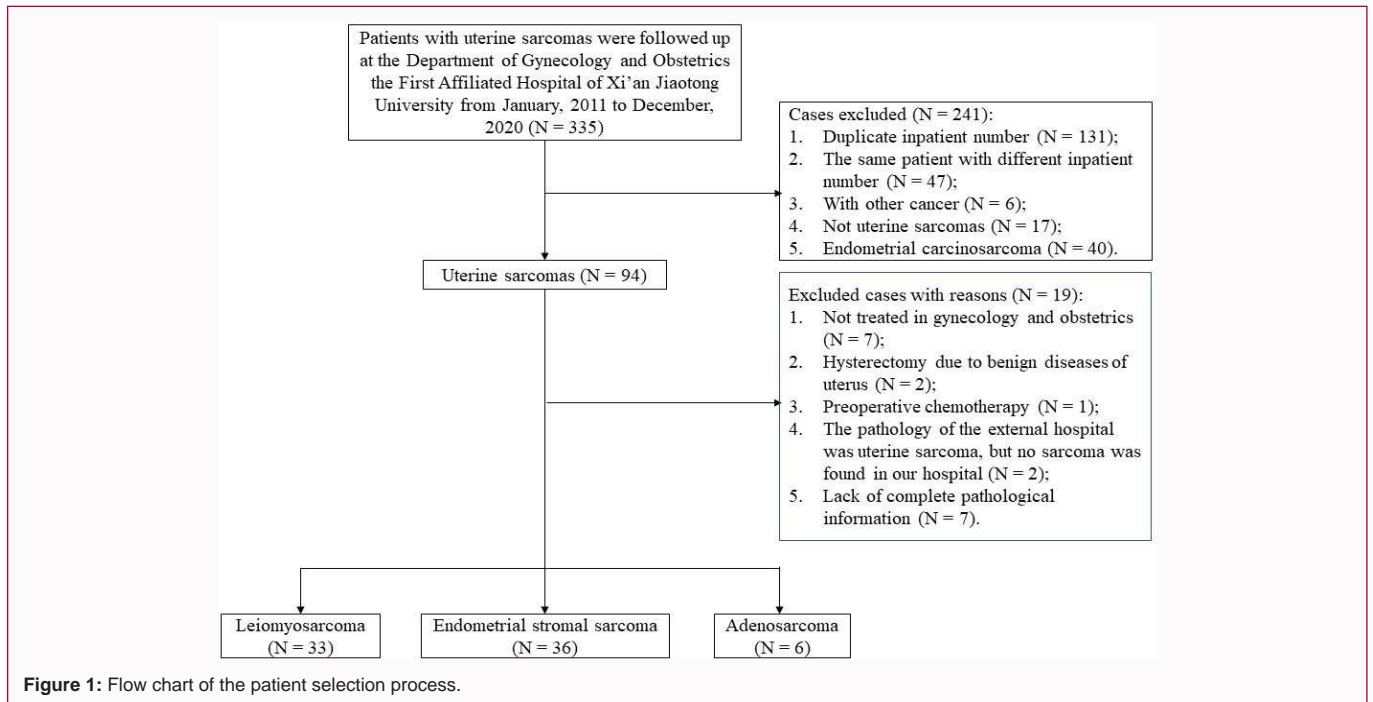
onset symptoms were irregular vaginal bleeding (56%, 42/75) and pelvic mass (29.3%, 22/75). Among 62 cases with complete data on CDFI, 39 (62.90%) had positive signals. Preoperative CA125 level was available for 59; 49(83.05%) had normal values. Surgical treatment was administered to 73 patients, with 68 (93.2%) patients, having total hysterectomy with TH-BSO, and 5 (6.8%) patients having total hysterectomy alone. Lymphadenectomy was performed in 24 patients, and only one LMS patient had lymph node metastasis with 9 months' survival. Based on FIGO staging, most patients (81.33%) were diagnosed as stage I. Most patients had adjuvant chemotherapy with 4 to 6 cycles after surgery (76.71%, 56/73) according to postoperative pathology including FIGO stage, histological grade, myometrial invasion, lymph node metastasis, LVSI and so on. The most common chemotherapy combination was paclitaxel and Platinum (PT) (64.29%, 36/56), followed by Ifosfamide + Epirubicin + Cisplatin (IAP) (26.79%, 15/56). A patient diagnosed with ESS received progesterone therapy without chemotherapy after surgery, with an OS of 47.5 months. For the remaining two patients, one patient refused any treatment because of old age and advanced stage, with an OS of 4.7 months. Another patient received radio-chemotherapy, with an OS of 15 months.

Univariate analysis of the total cohort

Among the total 75 patients, 26 (34.67%) patients recurred at the end of follow-up, with 25 dying from recurrence. Recurrence characterized as pelvic mass mostly occurred in pelvic cavity.

The mean PFS and OS were 89.41 (95% Confidence Interval (CI): 76.07-102.75) and 94.03 (95% CI: 81.67-106.38) months, respectively. The corresponding 5-year PFS and OS rates were 66.5% and 71%, respectively. Compared to patients in advanced stage (FIGO II-IV) patients in stage I had a significantly better prognosis, with longer PFS (98.6 vs. 38.2 months, P=0.001) and a higher 5-year PFS rate (74.7% vs. 27.3%, P=0.001). Similarly, stage I patients had significantly longer OS (103.8 vs. 49 months, P<0.001) and a higher 5-year OS rate (80% vs. 34.1%, P<0.001) compared to their advanced-stage counterparts.

Table 2 showed the comparisons of survival outcomes among various clinicopathological parameters and treatments of the total patients using the log-rank tests. The results revealed that diagnosis age >50 years, post-menopause, advanced stage and ≥ 1/2 myometrial invasion were associated with shorter PFS and OS (all P<0.05). In addition, LVSI was significantly linked with shorter OS (P<0.001) and marginally significantly shorter PFS (P=0.071).

Univariate analysis of subgroups

The subgroup analysis of our study differentiated between 36 cases of ESS, 33 LMS and 6 adenosarcomata. Univariate analysis was only performed for the ESS and LMS groups due to the small sample sizes of the adenosarcoma group, and the results were shown in Table 2.

In the ESS group, 31 patients were classified with stage I and 5 with stage II-IV. Eight (22.22%) patients underwent disease recurrence and 7 (19.44%) deaths reported at the last follow-up. The mean PFS and OS were 99.56 (95% CI: 84.48-114.63) and 103.69 (95% CI: 88.73-118.64) months, respectively. The corresponding 5-year PFS and OS rates were 80.4% and 84.9%, respectively. Univariate analysis showed that diagnosis age ≤ 50 years, pre-menopause, low-grade, <1/2 myometrial invasion, and absence of LVSI were associated with significantly longer PFS, and high-grade and LVSI were related to significantly shorter OS (all P<0.05). Age at diagnosis, menopausal state and myometrial invasion were not significantly associated with OS (P>0.05).

ESS included Low-Grade ESS (LG-ESS), High-Grade ESS (HG-ESS) and Undifferentiated Uterine Sarcoma (UUS) [1]. In our study, there were 21 cases of LG-ESS, 12 cases of HG-ESS,3 cases of unknown grade and 0 case of undifferentiated sarcoma. PFS was significantly higher in LG-ESS cohort (110.5 months) than that in HG-ESS (52 months) and UUS (21.2 months) (P=0.003). The OS was also significantly better in LG-ESS patients (118.03 months) than that for HG-ESS (56.4 months) and unknown group (26.2 months) (P=0.001). Meanwhile, patients with unknown grade uterine sarcoma

Table 1: General information about patients.

	Total (n=75)	ESS (n=36)	LMS (n=33)	Adenosarcoma (n=6)
Age at diagnosis (years)				
≤ 50	42	21	18	3
>50	33	15	15	3
Mean ± standard deviation	50.2 ± 10.7	49.9 ± 11.9	51.2 ± 9.8	46.8 ± 8.9
Median (range)	48 (31-81)	48 (31-81)	48 (35-73)	47 (34-57)
Menopausal state				
Premenopausal	49	23	23	3
Postmenopausal	26	13	10	3
Early symptom				
Irregular vaginal bleeding	42	23	13	6
Lower abdominal pain	8	3	5	0
Pelvic mass	22	9	13	0
Other	3	1	2	0
Preoperative CA125				
<35	49	22	21	6
≥ 35	10	6	4	0
miss	16	8	8	0
CDFI				
No	23	11	11	1
Yes	39	17	17	5
Miss	13	8	5	0
Initial diagnosis				
Uterine-fibroids	49	22	26	1
Uterine sarcoma	6	2	1	3
Other	20	12	6	2
Tumor size (cm)				
<5	14	9	1	4
≥ 5	48	21	25	2
Miss	13	6	7	0
FIGO Stage				
I	61	31	24	6
II-IV	11	5	6	0
Miss	3	0	3	0
Histological grade				
Low	35	21	13	1
High	23	12	8	3
Miss	17	3	12	2
Myometrial invasion				
<1/2	28	15	9	4
≥ 1/2	33	14	17	2
Miss	14	7	7	0
LVSI				
No	66	32	28	6
Yes	6	3	3	0
Miss	3	1	2	0

Treatment plan				
No treatment	1	0	1	0
Surgery	17	9	6	2
Surgery + adjuvant therapy	56	27	25	4
Adjuvant therapy	1	0	1	0
Lymphadenectomy				
No	49	25	21	3
Yes	24	11	10	3
Lymph node metastasis				
No	23	11	9	3
Yes	1	0	1	0
Chemotherapy regimen				
Paclitaxel + platinum	36	16	17	3
Ifosfamide + epirubicin + Cisplatin	15	7	7	1
Other	5	3	2	0
Disease recurrence	26	8	16	2
Died	25	7	16	2
PFS (months)				
Median	46.25	46.5	44.75	55.25
Range	6-132.3	6-125	7-132.3	6-96
OS (months)				
Median	50	49	50	55.25
Range	4.7-132.3	13-125	4.7-132.3	14-96

Note: LMS: Leiomyosarcoma; ESS: Endometrial Stromal Sarcoma; CA125: Carbohydrate Antigen 125; CDFI: Color Doppler Flow Imaging; FIGO: International Federation of Gynecology and Obstetrics; LVSI: Lymphovascular Space Invasion; PFS: Progression-Free Survival; OS: Overall Survival

showed the worst prognosis than the other two subtypes.

The LMS group included 24 patients with stage I, 6 with stage II-IV, and 3 unclassified. Recurrence and mortality were reported in 16 patients (48.48%, 16/33). The mean PFS and OS were 76.05 (95% CI: 55.87-96.23) and 83.46 (95% CI: 64.94-101.98) months, respectively. The 5-year PFS and OS rates were 52.2% and 58.3%, respectively. Univariate analysis identified that diagnosis age >51 years, post-menopause and advanced stage as predictors of shorter PFS and OS (P<0.05). Positive CDFI signal was significantly associated with decreased PFS (P<0.05) and marginally with reduced OS (P=0.098). Low-grade and <1/2 myometrial invasion were significantly associated with longer OS (P<0.05), while only marginally significantly associated with longer PFS. In addition, early symptoms were marginally significant predictors of prolonged PFS (P=0.092) and OS (P=0.05).

Comparatively, the ESS subgroup exhibited more favorable outcomes than those of the LMS group, including a significantly lower recurrence rate (22.22% *vs.* 48.48%, P=0.022), significantly longer PFS (99.56 *vs.* 76.05 months, P=0.043), and a trend towards longer OS (103.69 *vs.* 83.46 months, P=0.077), underscoring the variable prognosis and treatment response across uterine sarcoma.

Multivariable analysis

The results of the multivariable analysis were revealed in Table 3 and Figure 2, highlighting the independent prognostic risk factors

Table 2: Univariate analysis for PFS and OS using the log-rank tests in total cohort and subgroups.

	Total cohort						ESS						LMS					
	PFS			OS			PFS			OS			PFS			OS		
	5-year rate (%)	mean	P	5-year rate (%)	mean	P	5-year rate (%)	mean	P	5-year rate (%)	mean	P	5-year rate (%)	mean	P	5-year rate (%)	mean	P
All	66.5	89.41		71	94.03		80.4	99.56		84.9	103.69		52.2	76.05		58.3	83.46	
Age at diagnosis																		
≤ 50	80.6	105.7	0.004	82.7	110.3	0.005	90.5	115	0.022	88.8	114.6	0.108						
>50	46.9	62.6		55.1	73.8		66	77.5		80	92.9							
≤ 51													72.2	94.8	0.022	77.8	103.3	0.006
>51													15	37.5		24.4	47.7	
Menopausal state																		
Premenopausal	78.5	102.4	0.001	82.1	106.2	0.001	91.3	111.3	0.022	90.6	114.8	0.057	68.2	93	0.001	76.7	100	<0.001
Postmenopausal	41.1	50.3		45	55.3		60.6	48.5		74	55.1		0	23		0	31	
Early symptom																		
Vaginal bleeding	72.2	94.2	0.153	74.5	100.1	0.117	82.6	/	0.893	81.1	/	0.955	58.6	82.1	0.092	67.3	92.7	0.05
Abdominal pain	37.5	37.8		50	46		66.7	/		50	/		20	25.4		20	30.6	
Pelvic mass	66.6	82.6		73.5	86.7		77.8	/		88.9	/		61.4	78.7		68.6	83.5	
Other	66.7	33.7		50	35.8		100	/		/	/		50	28.3		50	35.8	
Preoperative CA125																		
<35	67.4	90.3	0.997	75.2	96.4	0.844	81.6	104.8	0.545	89.8	106.2	0.504	53.6	73.7	0.595	64.2	84.6	0.68
≥ 35	66.7	54		63.5	58.7		83.3	62.8		80	64		33.3	27.7		33.3	40	
Unknown	63.3	79.6		63.3	88.1		75	85.4		75	95.9		54.7	75.5		54.7	76.6	
CDFI																		
No	81.6	89.2	0.289	85.6	93.9	0.191	71.6	80.5	0.341	77.9	87.7	0.405	90	92.1	0.046	90	93.1	0.098
Yes	57.9	85.1		65.7	90.4		88.2	111.6		94.1	109.8		29.2	54.6		42.2	69.2	
Unknown	66.6	76.3		65.8	83.4		75	87.4		72.9	96.7		53.3	62.1		53.3	66.6	
Initial diagnosis																		
Uterine fibroids	67	91.6	0.497	72.4	97.4	0.446	77.3	89.8	0.24	80.2	94	0.222	57.2	80	0.791	65.2	88.6	0.473
Uterine sarcoma	66.7	47.3		33.3	50.7		50	28.5		50	33		0	53		0	53	
Other	74.7	91.6		76	93.8		91.7	109.4		100	111.4		50	43.3		41.7	46.7	
Tumor size (cm)																		
<5	92.9	94.7	0.093	92.9	95.3	0.2	100	/	0.277	100	/	0.406	100	/	0.31	100	/	0.499
≥ 5	54.1	80.7		61.7	86.6		71.4	/		79.5	/		40.3	/		49.1	/	
Miss	84.6	92.6		84.6	101.1		83.3	/		83.3	/		85.7	/		85.7	/	
FIGO Stage																		
I	74.7	98.6	0.001	80	103.8	0.001	83.6	103.1	0.177	85.4	109.4	0.252	67.8	94.4	<0.001	77.4	101	<0.001
II-IV	27.3	38.2		34.1	49		60	69		80	75.8		0	12.6		0	28.3	
Miss	0	24		0	31								0	24		0	31	
Pathological type																		
ESS	80.4	99.6	0.131	84.9	103.7	0.202	/	/		/	/		/	/		/	/	
LMS	52.2	76.1		58.3	83.5		/	/		/	/		/	/		/	/	
Adenosarcoma																		
	66.7	66		66.7	69.2		/	/		/	/		/	/		/	/	
Histologic grade																		
Low	79.6	99.1	0.137	86.2	104.7	0.097	90.2	110.5	0.003	94.1	118.3	0.001	60.6	74.4	0.059	71.6	80.1	0.026
High	52.2	59.8		53.1	62.7		75	52		82.5	56.4		0	27.7		0	37.5	
Miss	58.8	83.9		64.7	92.3		33.3	21.2		33.3	26.2		66.7	95.2		75	105.2	

Myometrial invasion																	
<1/2	92.2	116.3	0.001	96.4	122.3	0.001	100	120.3	0.016	100	124	0.064	88.9	114.8	0.069	100	127	0.012
≥ 1/2	44.8	55.1		52.8	62.2		57.1	59		70.1	67.1		35.3	48.1		41.2	55.8	
Unknown	74.1	82.7		69.4	80.9		85.7	92.7		85.7	93.1		53.3	32.3		40	34.4	
LVSI																	
No	67.3	90.6	0.071	72.2	95.4	<0.001	81	/	0.005	85.9	/	<0.001	54.1	79	0.178	60.8	87	0.103
Yes	66.7	73.5		66.7	75.2		100	/		/	/		33.3	28.2		33.3	31.5	
Miss	0	11		0	14		0	/		0	/							
Treatment plan																	
Surgery	50.7	/	0.615	48.2	/	0.305	81.8	59.7	0.999	81.8	60.5	0.554	25	39.8	0.32	25	47.2	0.212
Surgery + adjuvant therapy	68.9	/		75.7	/		80	99.6		86.9	105.7		58.4	81.4		66.1	88.9	
Lymphadenectomy																	
No	62.6	85.6	0.478	69.7	91.4	0.636	79.8	91.9	0.899	87.2	93.3	0.992	43.9	66.4	0.203	53.6	78.3	0.435
Yes	75	91.8		74.1	97.3		81.8	99.1		80.8	105.2		70	81.5		68.6	81.7	
Chemotherapy regimen																	
IAP	51.4	56.9	0.241	64	64.2	0.224	71.4	/	0.74	80	/	0.909	42.9	45.7	0.464	57.1	53.5	0.218
PT	77	100		82.1	105.9		81.3	/		87.5	/		68.2	91.6		72.7	100.5	
Other	75	31.1		75	32.6		100	/		/	/		50	16.8		50	19.8	

Note: & age categorization was based on the mean age of each group

PFS: Progression-Free Survival; OS: Overall Survival; CA125: Carbohydrate Antigen 125; CDFI: Color Doppler Flow Imaging; FIGO: International Federation of Gynecology and Obstetrics; LMS: Leiomyosarcoma; ESS: Endometrial Stromal Sarcoma; LVSI: Lymphovascular Space Invasion; IAP: Ifosfamide + epirubicin + Cisplatin; PT: Paclitaxel + Platinum

Table 3: Multivariate analysis for PFS and OS using Cox-proportional hazards regression models in total cohort and subgroups.

Cohort			HR	95% CI	P
Total	**PFS**	Menopause state	3.861	1.65-9.02	0.002
		FIGO stage	3.418	1.72-6.79	<0.001
	OS	Menopause state	3.703	1.54-8.91	0.003
		FIGO stage	3.498	1.68-7.27	0.001
Subgroups					
ESS	**PFS**	Age at diagnosis	5.627	1.09-29.06	0.039
		Histologic grade	4.66	1.32-16.48	0.017
	OS	Menopause state	8.252	0.78-87.46	0.08
		Histologic grade	8.349	1.58-44.13	0.012
		Lymphovascular space invasion	11.266	1.67-76.22	0.013
LMS	**PFS**	Menopause state	4.595	1.50-14.05	0.007
		FIGO stage	3.376	1.46-7.82	0.005
	OS	Menopause state	6.078	1.69-21.80	0.006
		FIGO stage	3.829	1.44-10.17	0.007

affecting survival within our patient cohort. For the entire cohort, post-menopause (HR=3.861, 95% CI: 1.65-9.02, P=0.002 for PFS and HR=3.703, 95% CI: 1.54-8.91, P=0.003 for OS) and advanced stage (HR=3.418, 95% CI: 1.72-6.79, P<0.001 for PFS and HR=3.498, 95% CI: 1.68-7.27, P=0.001 for OS) were independent prognostic risk factors for survival.

Similarly, in the LMS subgroup analysis, post-menopause (HR=4.595, 95% CI: 1.50-14.05, P=0.007 for PFS and HR=6.078, 95% CI: 1.69-21.80, P=0.006 for OS) and advanced stage (HR=3.376, 95% CI: 1.46-7.82, P=0.005 for PFS and HR=3.829, 95% CI: 1.44-10.17, P=0.007 for OS) were independent prognostic risk factors of survival, underscoring similar patterns of risk across different sarcoma types.

For the ESS group, diagnosis age >50 years (HR=5.627, 95% CI: 1.09-29.06, P=0.039) and high-grade (HR=4.660, 95% CI: 1.32-16.48, P=0.017) were found to be independent risk factors of influencing PFS. Furthermore, high-grade (HR=8.349, 95% CI: 1.58-44.13, P=0.012) and the presence of LVSI (HR=11.266, 95% CI: 1.67-76.22, P=0.013) were identified as independent risk factors of OS.

These findings suggested that certain clinicopathological features, particularly menopausal status, disease stage, histological grade and LVSI, played a critical role in predicting the prognosis of patients with uterine sarcoma.

Discussion

Evidence shows that the recurrence rate for uterine sarcoma is high, the prognosis is hopeless, and the preoperative diagnosis is difficult due to non-specific symptoms and the limitation of diagnosis [1]. Previous western studies, conducted almost entirely including carcinosarcoma, explored the relationships between risk factors, adjuvant treatments, and survival based on traditional classification systems [12-16]. However, there have been a few studies with respect to them in China and the patient grouping studied by newer classifications excluding carcinosarcoma. In addition, the incidence of uterine sarcoma varies by race and is higher in African-Americans than in other racial groups [3,17]. Our research presented is a comprehensive analysis of uterine sarcoma and examines 75 Chinese patients over a 10-year period using the latest classification system for more detailed results.

Our findings revealed that LMS had a poorer prognosis than that of ESS. Specifically, for the ESS group, we determined post-menopausal, high-grade and LVSI as key factors associated with reduced survival. Furthermore, the study highlighted the potential diagnostic value of CDFI, enabling it to distinguish between benign and malignant tumors and representing a new research topic.
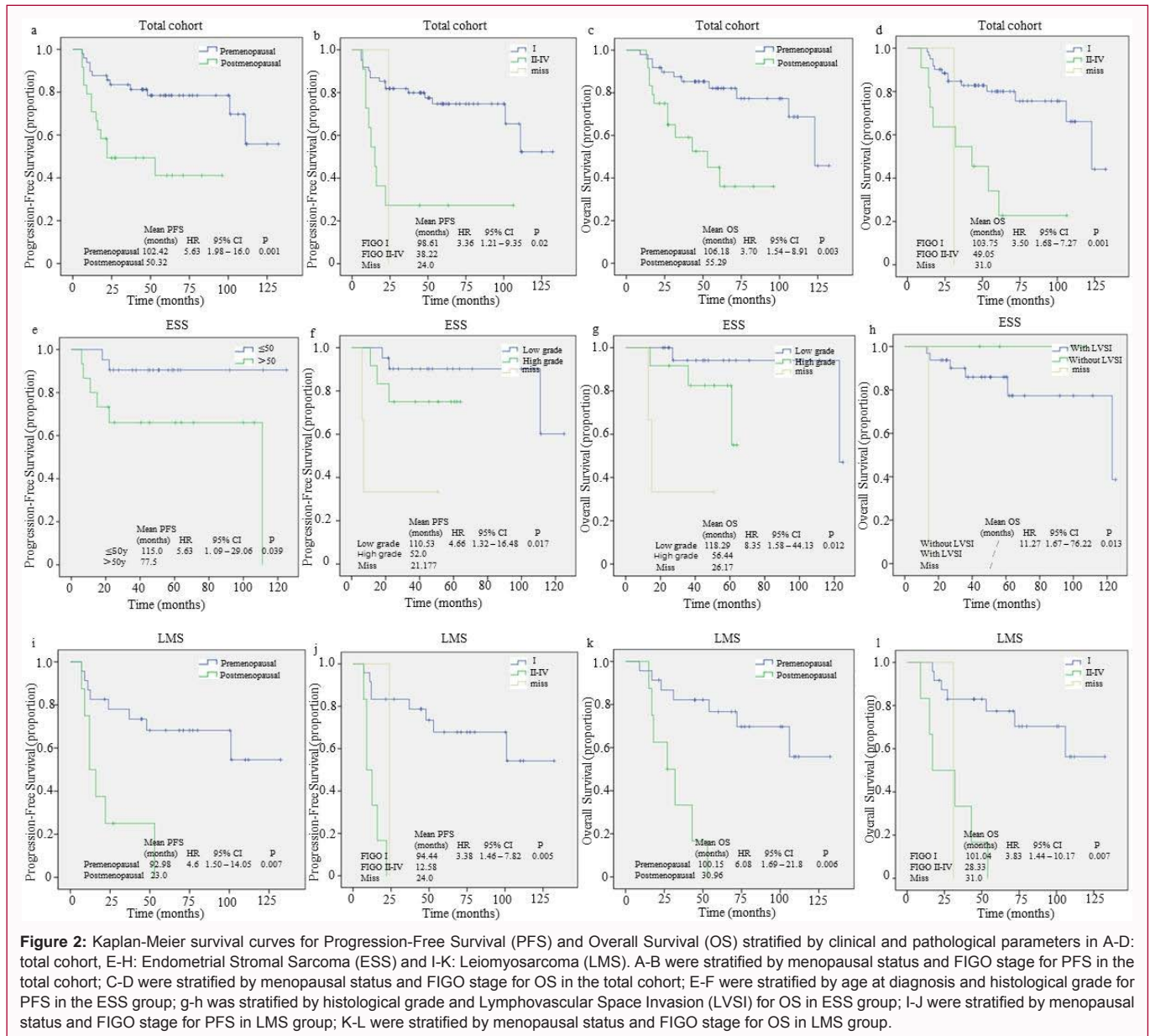
Figure 2: Kaplan-Meier survival curves for Progression-Free Survival (PFS) and Overall Survival (OS) stratified by clinical and pathological parameters in A-D: total cohort, E-H: Endometrial Stromal Sarcoma (ESS) and I-K: Leiomyosarcoma (LMS). A-B were stratified by menopausal status and FIGO stage for PFS in the total cohort; C-D were stratified by menopausal status and FIGO stage for OS in the total cohort; E-F were stratified by age at diagnosis and histological grade for PFS in the ESS group; g-h was stratified by histological grade and Lymphovascular Space Invasion (LVSI) for OS in ESS group; I-J were stratified by menopausal status and FIGO stage for PFS in LMS group; K-L were stratified by menopausal status and FIGO stage for OS in LMS group.

Our study revealed ESS as the most common subtype, comprising 48% of the total patients, which was in line with prior studies on the clinical characteristics of uterine sarcoma in China [18], but contradicting the fact that LMS was the most frequent one [19]. The difference in inclusion criteria may lead to the above divergence. Univariate analysis showed that over 50 years, post-menopause, advanced stage and ≥ 1/2 myometrial invasion were significantly associated with poorer survival; while multivariable analysis demonstrated that post-menopause and advanced stage were independent prognostic factors for survival of the total cohort and the LMS group. These findings were consistent with previous studies showing higher incidence and poorer prognosis in postmenopausal, >50 aged [20,21] and advanced-staged women, [14,22] who were not limited by race or traditional classification systems.

Studies showed that prognoses of different pathological types of uterine sarcoma varied a lot [23-26]. Prognosis was much better without muscle infiltration or excessive hyperplasia of sarcoma [25]. Low-grade ESS grew slowly and had a good prognosis in initial stages than that of high-grade ESS in our study. However, there is currently a lack of effective molecular markers to identify high-grade and low-grade ESS, and our study also lacks exploration on relevant molecular markers. Francesca Micci's study elucidated the existence of chromosomal rearrangement between different grades of ESS [27], which might provide a new direction for the diagnosis. Kommoss reported the amplification of the *MDM2* gene in HG-ESS with BCOR-rearrangement, which provided the targeted therapy for the subset of HG-ESS [28].

Our study showed that ESS had a significantly lower recurrence and a higher 5-year survival rate than LMS, which was in agreement with previous studies [29,30]. Women from different cultures could have different attitudes towards body discomfort, which might impact its outcome. Muslim women in particular who have irregular bleeding would care more about prayer; disruptive flow led to an early intervene, treatment and hasty hysterectomy, which may be contributing to the relatively higher survival rates regarding ESS [31]. Otherwise, LMS often present with the same symptoms

as leiomyomas, and cannot reliably be distinguished clinically [4]. Misdiagnosis of LMS as uterine leiomyoma and delayed treatment due to minimally invasive therapy and inadvertent dissemination [32].

Diagnosing uterine sarcoma is generally difficult due to unspecific early symptoms, such as irregular vaginal bleeding (the most common), abdominal pain, and pelvic mass [4]. Ultrasound is a useful diagnostic tool for uterine disease among women with uterine bleeding. In our research, 62.9% of patients had CDFI during the examination. In the LMS group, patients with CDFI--positive signals had significantly shorter PFS and marginally significantly shorter OS. This suggests the potentially important role of CDFI in the evaluation of the malignant transformation of uterus myoma, which is similar to a finding reported by Yang Hua [33]. Asim Kurjak reported that transvaginal color Doppler ultrasound could distinguish uterine sarcoma from uterus myoma by using a cutoff in resistance index of 0.4 of tumoral blood vessels [34]. This cutoff showed a diagnostic value of 90.91% for sensitivity, 99.82% for specificity, 71.43% for positive predictive value and 99.96% for negative predictive value, respectively [34]. However, the study had small sample sizes (n=10). Further studies are needed to figure out the clinical significance of the resistance index of tumor blood flow for uterine sarcoma. Other studies also demonstrated that LMS frequently displayed areas of high signal intensity on T1-weighted images [35] and b-value DWI36 and lower apparent diffusion coefficient value 37 compared with leiomyomas. They provide a new direction for distinguishing uterine sarcoma form uterine fibroids.

The role of adjuvant chemotherapy is controversial in the management of uterine sarcoma. Some studies [11,38-40] reported that chemotherapy was effective for uterine sarcoma and decreased the risk of metastasis. Some researchers found that adjuvant chemotherapy was associated with decreased survival [12,41], while others showed better pelvic control and survival rate in adjuvant chemotherapy after surgery [11,14,42]. In our cohort, 76.7% of patients received chemotherapy or chemoradiotherapy after surgery, yet adjuvant therapy didn't affect their survival, which was similar to previous studies [43-45]. This controversy may be due to the large proportion of FIGO I stage patients and the small sample sizes of our cohort. In the future, more clinical trials are needed to verify the effect of adjuvant chemotherapy on the survival of uterine sarcoma.

Compared with previous studies, our investigation is distinctive in several aspects. (1) Our study is based on certain Chinese patients in a way. It thus considerably complements the currently available literatures that focus on the clinicopathological features and prognosis of uterine sarcomas conducted in Western population. It significantly increases the global knowledge database regarding potential ethnic and geographic differences in sarcomas. (2) This study uses the new classification of uterine sarcomas from 2003 in an attempt to provide an up-to-date exploration of their clinicopathological characteristics and prognosis. (3) Given the evident heterogeneity within uterine sarcomas, subgroup analysis was performed separately and most survival factors were developed for each sarcoma group, namely ESS and LMS respectively. (4) The usage of CDFI, as a potential malignant myoma indicator, offer an innovation that it may play an important role in novel non-invasive diagnostic techniques.

Our study had some limitations. First, the small sample sizes of adenosarcoma limit the statistical power and generalizability of the findings. This constraint makes it challenging to conduct comprehensive subgroup analyses or to conclude the prognostic implications for rare sarcoma types definitively. Second, the retrospective nature of the study design made it subject to selection and recall bias. These biases could affect accuracy of the collected data and interpretation of the study's findings. Third, the study was performed in a single center. Its findings may not be broadly applicable to all populations. Forth, the study suggests CDFI as potentially valuable tool for identifying malignant myomas, which is preliminary and requires further validation through larger, prospective studies to determine its clinical utility and accuracy.

Conclusion

According to our results, LMS is more aggressive than ESS. Post-menopause and advanced stage is independent risk factors of survival for the total patients and LMS, which were not limited to race or traditional classification system. Meanwhile, post-menopause, high-grade and LVSI are independently related to decreased survival in the ESS group. Uterine myoma with blood flow signal may be a useful indicator of malignant myoma, which needs to further validate its diagnostic utility in large-scale, multi-center studies and refine protocols for the management of uterine sarcomas.

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