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Contents

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GUIDELINES

1756 French Spine Surgery Society guidelines for management of spinal surgeries during COVID-19 pandemic
Prost S, Charles YP, Allain J, Barat JL, d'Astorg H, Delhaye M, Eap C, Zairi F, Guigui P, Ilharreborde B, Meyblum J, Le Huec JC, Lonjon N, Lot G, Hamel O, Riouallon G, Litrico S, Tropiano P, Blondel B, the French Spine Surgery Society

OPINION REVIEW

1763 Needs and concerns of patients in isolation care units - learnings from COVID-19: A reflection
Fan PEM, Aloweni F, Lim SH, Ang SY, Perera K, Quek AH, Quek HKS, Ayre TC

REVIEW

1767 Prophylactic and therapeutic roles of oleanolic acid and its derivatives in several diseases
Sen A

1793 Macrophage regulation of graft-*vs*-host disease
Hong YQ, Wan B, Li XF

MINIREVIEWS

1806 Antiphospholipid syndrome and its role in pediatric cerebrovascular diseases: A literature review
Sarecka-Hujar B, Kopyta I

1818 Remotely monitored telerehabilitation for cardiac patients: A review of the current situation
Batalik L, Filakova K, Batalikova K, Dosbaba F

1832 Keystone design perforator island flap in facial defect reconstruction
Lim SY, Yoon CS, Lee HG, Kim KN

ORIGINAL ARTICLE

Clinical and Translational Research

1848 Cross electro-nape-acupuncture ameliorates cerebral hemorrhage-induced brain damage by inhibiting necroptosis
Cai GF, Sun ZR, Zhuang Z, Zhou HC, Gao S, Liu K, Shang LL, Jia KP, Wang XZ, Zhao H, Cai GL, Song WL, Xu SN

Retrospective Study

1859 Evaluation of ischemic lesions after carotid artery stenting with diffusion-weighted imaging
Beyhan M, Acu B, Gökçe E, Fırat MM

1871 Transjugular intrahepatic portosystemic shunt and splenectomy are more effective than endoscopic therapy for recurrent variceal bleeding in patients with idiopathic noncirrhotic portal hypertension
He FL, Qi RZ, Zhang YN, Zhang K, Zhu-Ge YZ, Wang M, Wang Y, Jia JD, Liu FQ

1878 Ligliptin for treatment of type 2 diabetes mellitus with early renal injury: Efficacy and impact on endogenous hydrogen sulfide and endothelial function
Zhang J, Du YL, Zhang H, Sui H, Hou WK

1887 Outcomes of patients with pelvic leiomyosarcoma treated by surgery and relevant auxiliary diagnosis
Sun Q, Yang X, Zeng Z, Wei X, Li KZ, Xu XY

1897 Defecation function and quality of life in patients with slow-transit constipation after colectomy
Tian Y, Wang L, Ye JW, Zhang Y, Zheng HC, Shen HD, Li F, Liu BH, Tong WD

1908 Risk factors, incidence, and morbidity associated with antibiotic-associated diarrhea in intensive care unit patients receiving antibiotic monotherapy
Zhou H, Xu Q, Liu Y, Guo LT

Observational Study

1916 Serum von Willebrand factor for early diagnosis of lung adenocarcinoma in patients with type 2 diabetes mellitus
Zhou YY, Du X, Tang JL, Wang QP, Chen K, Shi BM

1923 Four-microRNA signature for detection of type 2 diabetes
Yan LN, Zhang X, Xu F, Fan YY, Ge B, Guo H, Li ZL

CASE REPORT

1932 Isolated colonic neurofibroma, a rare tumor: A case report and review of literature
Ghoneim S, Sandhu S, Sandhu D

1939 Helmet-based noninvasive ventilation for acute exacerbation of chronic obstructive pulmonary disease: A case report
Park MH, Kim MJ, Kim AJ, Lee MJ, Kim JS

1944 Appendectomy in patient with suspected COVID-19 with negative COVID-19 results: A case report
Kim C, Kim JK, Yeo IH, Choe JY, Lee JE, Kang SJ, Park CS, Kwon KT, Hwang S

1950 T4 cervical esophageal cancer cured with modern chemoradiotherapy: A case report
Lee CC, Yeo CM, Ng WK, Verma A, Tey JC

1958 Lumbar disc rehydration in the bridged segment using the BioFlex dynamic stabilization system: A case report and literature review
Li YC, Feng XF, Pang XD, Tan J, Peng BG

1966 Traditional investigation and management for recurrent hemarthrosis after total knee arthroplasty: A case report
Geng X, Li Y, He X, Tian H

1973 Positron emission tomography/computed tomography findings of multiple cystic lymphangiomas in an adult: A case report
Sun MM, Shen J

1979 Heterotopic pancreas adenocarcinoma in the stomach: A case report and literature review
Xiong Y, Xie Y, Jin DD, Wang XY

1988 Early-onset refractory diarrhea due to immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome associated with a novel mutation in the *FOXP3* gene: A case report
Su N, Chen C, Zhou X, Ma GD, Chen RL, Tian C

1995 Tuberous sclerosis complex presenting as primary intestinal lymphangiectasia: A case report
Lin WH, Zhang ZH, Wang HL, Ren L, Geng LL

2001 Gilbert's syndrome coexisting with hereditary spherocytosis might not be rare: Six case reports
Kang LL, Liu ZL, Zhang HD

2009 Effective combined therapy for pulmonary epithelioid hemangioendothelioma: A case report
Zhang XQ, Chen H, Song S, Qin Y, Cai LM, Zhang F

2016 Unexplained huge liver infarction presenting as a tumor with bleeding: A case report
Wang FH, Yang NN, Liu F, Tian H

2023 Rare recurrent gallstone ileus: A case report
Jiang H, Jin C, Mo JG, Wang LZ, Ma L, Wang KP

2028 Treating severe periodontitis with staged load applied implant restoration: A case report
Wang SH, Ni WC, Wang RF

2038 Cryptococcal pneumonia in a human immunodeficiency virus-negative patient: A case report
Jiang XQ, Zhang YB

2044 Ileocecal intussusception caused by two different tumors - which is the culprit lesion? A case report
Fan WF, Ma G, Li GC, Long J, Xu YH, Guo KJ, Liu Z

2050 Robot-assisted retroperitoneal laparoscopic excision of perirenal vascular tumor: A case report
Zhang C, Fu B, Xu S, Zhou XC, Cheng XF, Fu WQ, Wang GX

2056 Successful use of plasma exchange in fulminant lupus myocarditis coexisting with pneumonia: A case report
Xing ZX, Yu K, Yang H, Liu GY, Chen N, Wang Y, Chen M

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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ORIGINAL ARTICLE

Retrospective Study

Outcomes of patients with pelvic leiomyosarcoma treated by surgery and relevant auxiliary diagnosis

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Author contributions: Sun Q and Yang X designed and performed the research; Wei X and Zeng Z conceptualized the study and analyzed the clinical data; Li KZ and Xu XY supervised the study; Sun Q and Yang X contributed equally to this work; all authors approved the submitted version.

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Abstract

BACKGROUND

Leiomyosarcoma is a subtype of soft tissue sarcoma with adverse outcomes. Leiomyosarcoma accounts for nearly 70% of all uterine sarcomas and is responsible for a considerable proportion of deaths because of uterine cancer. Clinical characteristics and relevant diagnosis of pelvic leiomyosarcoma should be further explored.

AIM

To identify the outcome and relevant perioperative evaluation of patients with pelvic leiomyosarcoma.

METHODS

The Kaplan-Meier method was used to determine progression-free survival and overall survival rates. Factors predictive of outcomes were identified using univariate and multivariate Cox proportional hazards models.

RESULTS

Fifty-one patients with pelvic leiomyosarcoma were enrolled and divided into two groups including uterine leiomyosarcoma and non-uterine leiomyosarcoma. Overall, 28.6% and 45.5% of uterine leiomyosarcoma and non-uterine leiomyosarcoma patients, respectively, had elevated carbohydrate antigen 125 levels, whereas 45.7% and 68.8%, respectively, underwent ultrasonography. Although 68.8% of uterine leiomyosarcoma patients were initially diagnosed with hysteromyoma, 72.7% of non-uterine leiomyosarcoma patients had pelvic and abdominal masses. Moreover, 93.3% of the recurrent lesions were detected using ultrasonography. Patients with International Federation of Gynaecology and Obstetrics (FIGO) stages III–IV disease had poorer progression-free survival values than those with FIGO stages I–II (P = 0.027) disease. FIGO stage was significantly associated with poor progression-free survival in the univariate (hazard ratio = 2.64, P = 0.03) and multivariate (hazard ratio = 2.49, P = 0.048)

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analyses.

CONCLUSION
Serum tumour biomarkers cannot be used for pelvic leiomyosarcoma diagnosis. FIGO stage is critical to predict the outcome of uterine leiomyosarcoma. Ultrasonography is more reliable for postoperative follow-up than preoperative diagnosis.

Key words: Uterine leiomyosarcoma; Non-uterine leiomyosarcoma; Serum biomarker; Prognosis; Ultrasonography

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Core tip: Owing to a lack of long-term leiomyosarcoma-focused studies, the clinical features of pelvic leiomyosarcoma among women remain unclear. Our study showed that serum tumour biomarkers cannot be used for pelvic leiomyosarcoma diagnosis and ultrasonography is more reliable for postoperative follow-up than preoperative diagnosis.

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INTRODUCTION

Leiomyosarcoma is a subtype of soft tissue sarcoma that is derived from smooth muscles located in the uterus and soft tissue. The most frequently involved organs are the retroperitoneal space, extremities, and uterus. Despite its low annual incidence (approximately 0.36–0.64 per 100000 women), leiomyosarcoma accounts for nearly 70% of all uterine sarcomas and is responsible for a considerable proportion of deaths because of uterine cancer[1-3]. Leiomyosarcoma can occur at any site, but it occurs most commonly in the retroperitoneum and proximal extremities[4,5]. However, there is a lack of convincing data on pelvic non-uterine leiomyosarcoma[6], and the biological behaviour of this tumour type, including the associated metastases and prognoses, requires further exploration.

Although various diagnostic tools have been used to preoperatively evaluate uterine leiomyosarcoma, they have a low sensitivity for differentiating uterine leiomyosarcoma from fibroids; a previous study revealed that only approximately 54% of uterine leiomyosarcoma lesions were unidentified before surgery[7]. Moreover, unlike in the case of ovarian cancer, regular serum tumour markers have limited value in diagnosing uterine leiomyosarcoma[8-10]. Of all auxiliary examinations, only medical imaging can identify the existence and position of lesions. Computed tomography, magnetic resonance imaging, positron emission tomography, and ultrasonography can be used in the examination and follow-up of leiomyosarcoma patients[11-13].

The treatment methods and prognostic factors related to leiomyosarcoma require extensive research because of the disease's high malignant potential. Previous studies have confirmed that the standard surgical resection of uterine leiomyosarcoma is associated with improved prognoses[12,14]. Lymphadenectomy is recommended following the intraoperative discovery of palpable lymph nodes in women with extrauterine disease[15,16]. Recent studies have implied that tumour stage, size, and relapse status, and mitotic index are associated with overall survival and progression-free survival in uterine leiomyosarcoma[17-19]. Furthermore, the disease stage at diagnosis is an important predictor of survival[20,21]. However, there is a lack of standardised treatment guidelines and specialised investigations focusing on non-uterine leiomyosarcoma of the pelvic cavity. Studies that compared the clinical differences have not shown consistent results[4,22]. Thus, there is an urgent need to identify clinical characteristics of non-uterine leiomyosarcoma to provide early diagnosis and proper treatment.

Owing to a lack of long-term leiomyosarcoma-focused studies, the clinical and

ultrasonographic features of uterine leiomyosarcoma and non-uterine leiomyosarcoma among women remain unclear. Therefore, we retrospectively analysed patients with uterine leiomyosarcoma and non-uterine leiomyosarcoma to identify their clinical characteristics in detail.

MATERIALS AND METHODS

Fifty-one patients treated between 2000 and 2018 were retrospectively examined in our study; the patients included 35 (68.6%) with uterine leiomyosarcoma and 16 (31.4%) with non-uterine leiomyosarcoma. The study was approved by the Ethical Committee of the Medical Faculty of Tongji Medical College, and verbal informed consent was obtained from the participants or their relatives. The tumour stages were evaluated based on International Federation of Gynaecology and Obstetrics (FIGO) criteria[23]. The outcomes included progression-free survival and overall survival; progression-free survival was calculated from the surgery date when the diagnosis was first confirmed to the date of detection of recurrence *via* imaging examination. Overall survival was calculated from the date of surgery that first confirmed the diagnosis to the date of death or that of the last follow-up for survivors.

Statistical analysis

The overall survival and progression-free survival of patients were estimated using Kaplan-Meier curves, and differences between uterine leiomyosarcoma and non-uterine leiomyosarcoma patients were compared using a log-rank test. Pearson's χ^2 test or Fisher's exact test was used to assess the association among clinicopathologic features. Statistical significance and differences in survival were assessed using the Cox proportional hazards regression model. Factors with P values < 0.05 in the univariate analysis were included in the multivariate Cox regression analysis. For all analyses, the level of statistical significance was set at $P < 0.05$. Data analyses were performed using the Statistical Product and Service Solutions software (SPSS, version 22.0; IBM Corp., Armonk, NY, United States).

RESULTS

Descriptive characteristics of leiomyosarcoma patients

Fifty-one women with leiomyosarcoma were enrolled and were divided into the uterine leiomyosarcoma and non-uterine leiomyosarcoma groups based on tumour origin. Thirty-five (68.6%) patients were classified as having uterine leiomyosarcoma, whereas 16 (31.4%) had non-uterine leiomyosarcoma. We followed 43 women till May 2019. The patients' characteristics are shown in Table 1. The mean ages of the patients in the uterine leiomyosarcoma and non-uterine leiomyosarcoma groups were 49.6 (range, 32-71) years and 46 (range, 29-66) years, respectively. The majority of the patients in both the groups initially presented with menopause (60% in the uterine leiomyosarcoma group and 56.3% in the non-uterine leiomyosarcoma group). Other medical conditions such as hypertension and diabetes mellitus were rarely observed, with < 20% of the patients presenting with these two disorders. Initial symptoms were particularly important for patient diagnoses. A plurality of patients with uterine leiomyosarcoma (45.7%) did not state obvious symptoms, and their lesions were diagnosed during medical examination. Furthermore, 25.7% of the patients with uterine leiomyosarcoma sought medical advice for menorrhagia and menstrual disorders, which were the most frequently reported complaints. Additionally, 17.1% of the patients with uterine leiomyosarcoma complained of abdominal pain and distention, and 5.7% had a palpable mass and postmenopausal bleeding. In contrast, 50% of patients with non-uterine leiomyosarcoma presented with abdominal pain and abdominal distention, whereas other complaints were rarely reported.

Serum tumour markers and medical imaging examinations

The levels of serum tumour markers, *i.e.*, carbohydrate antigen (CA)125, alpha-fetoprotein, carcinoembryonic antigen (CEA), CA199, CA153, and CA724, were assessed for their potential association with leiomyosarcoma considering their roles in other malignant gynaecological diseases[8,24,25]. Because of our study's long time span, only a proportion of our patients underwent serum tumour marker screening (Table 2). Most patients were screened for CA125 levels (60% in the uterine leiomyosarcoma group and 68.8% in the non-uterine leiomyosarcoma group); however, the CA125 positive rates were not high in either group. Only 28.6% and 45.5% of patients in the uterine leiomyosarcoma and non-uterine leiomyosarcoma groups, respectively, had

Table 1 Basic demographic characteristics of patients

Characteristic	Uterine leiomyosarcoma (*n* = 35)	Non-uterine leiomyosarcoma (*n* = 16)
Age [mean (range)], yr	49.6 (32-71)	46.0 (29-66)
Menopause, *n* (%)		
No	21 (60)	9 (56.3)
Yes	14 (40)	7 (43.7)
Medical disease, *n* (%)		
Hypertension	6 (17.1)	2 (12.5)
Diabetes mellitus	1 (2.9)	2 (12.5)
History of operation, *n* (%)		
Hysteromyoma surgery	20 (57.1)	6 (37.5)
Cesarean section	5 (14.3)	3 (18.8)
Other abdominal surgeries[1]	8 (22.9)	6 (37.5)
Clinical symptoms, *n* (%)		
Menorrhagia and menstrual disorder	9 (25.7)	0 (0)
Abdominal pain and abdominal distention	6 (17.1)	8 (50)
Palpable mass	2 (5.7)	1 (6.25)
Limb pain	0 (0)	1 (6.25)
Postmenopausal bleeding	2 (5.7)	1 (6.25)
No obvious discomfort and examination revealed abnormalities	16 (45.7)	4 (25)
Ascites, *n* (%)		
Increased	5 (14.3)	2 (12.5)
Normal	30 (85.7)	14 (87.5)
Number of pregnancies [mean (range)], *n* (%)	2.86 (0-6)	3.31 (2-6)
FIGO stage, *n* (%)		
I	16 (45.7)	–
II	4 (11.4)	–
III	9 (25.7)	–

[1]Including appendicectomy, tubal sterilization, and cholecystectomy. FIGO: International Federation of Gynaecology and Obstetrics.

elevated CA125 levels. Of the 42.9% and 63.6% of uterine leiomyosarcoma and non-uterine leiomyosarcoma patients, respectively, whose CEA levels were assessed, only one uterine leiomyosarcoma patient had elevated levels (with no non-uterine leiomyosarcoma patient having such elevations). Moreover, the alpha-fetoprotein and CA199 levels were normal in both groups. Only a minority of patients with uterine leiomyosarcoma underwent CA153 and CA724 screening; none of the patients had elevated CA153 levels and two had elevated CA724 levels, accounting for 40% of all the examined patients. These observations demonstrate that serum tumour markers have limited ability in leiomyosarcoma diagnosis; therefore, we next examined the medical imaging findings.

Ultrasonography was the most widely performed procedure and was performed in 45.7% and 68.8% of patients in the uterine leiomyosarcoma and non-uterine leiomyosarcoma groups, respectively. However, the majority of the patients with uterine leiomyosarcoma (68.8%) were diagnosed with hysteromyoma, whereas the majority of patients with non-uterine leiomyosarcoma (72.7%) were diagnosed with pelvic and abdominal masses. These data imply that ultrasonography has limited ability in distinguishing between benign and malignant foci.

Comparison of prognoses between uterine leiomyosarcoma and non-uterine leiomyosarcoma

We followed 43 patients, including 29 with uterine leiomyosarcoma (67.4%) and 14 with non-uterine leiomyosarcoma (32.6%). In the Kaplan-Meier analysis, no significant differences were found in the progression-free survival (P = 0.54) and overall survival values (P = 0.97) between patients in the uterine leiomyosarcoma and non-uterine leiomyosarcoma groups (Figure 1A and 1B). Because FIGO stage is a known prognostic indicator[26], we divided uterine leiomyosarcoma patients into the early and late-stage groups and compared their survival curves with those of non-uterine leiomyosarcoma patients. We found significant differences in progression-free

Table 2 Serum tumor markers and medical imaging examinations of pelvic leiomyosarcoma patients

Characteristic	Uterine leiomyosarcoma (*n* = 35)	Non-uterine leiomyosarcoma (*n* = 16)
Serum tumor markers, *n* (%)		
CA125	21 (60)	11 (68.8)
Elevated	6 (28.6)	5 (45.5)
Not elevated	15 (71.4)	6 (54.5)
CEA	15 (42.9)	7 (63.6)
Elevated	1 (6.7)	0 (0)
Not elevated	14 (93.3)	7 (100)
AFP	14 (40)	7 (63.6)
Elevated	0 (0)	0 (0)
Not elevated	14 (100)	7 (100)
CA199	12 (34.3)	7 (63.6)
Elevated	0 (0)	0 (0)
Not elevated	12 (100)	7 (100)
CA153	5 (14.3)	0 (0)
Elevated	0 (0)	–
Not elevated	5 (100)	–
CA724	5 (14.3)	0 (0)
Elevated	2 (40)	–
Not elevated	3 (60)	–
Medical imaging examination, *n* (%)		
Ultrasonography	16 (45.7)	11 (68.8)
Hysteromyoma	11 (68.8)	1 (9.1)
Pelvic and abdominal mass	4 (25)	8 (72.7)
Malignant occupancy of cervix	1 (6.2)	2 (18.2)
CT	2 (5.7)	1 (6.3)
MRI	1 (2.9)	0 (0)

CA: Carbohydrate antigen; CEA: Carcinoembryonic antigen; CT: Computed tomography; MRI: Magnetic resonance imaging.

survival values (P = 0.027) between the early- and late-stage groups (Figure 1C); however, this did not apply to overall survival (Figure 1D).

Clinical factors associated with leiomyosarcoma prognosis

We incorporated various clinical characteristics to identify factors that affected the prognosis of patients with leiomyosarcoma. In the univariate Cox regression analysis, FIGO stage (uterine leiomyosarcoma I–II *vs* III–IV: Hazard ratio = 2.64, P = 0.03), chemotherapy (hazard ratio = 2.95, P = 0.03), and neoplasm metastasis (hazard ratio = 3.31, P = 0.006) were independent factors that were significantly related to poor progression-free survival. Factors with P values < 0.05 in the univariate analysis were included in the multivariate Cox regression analysis. Because collinearity existed between FIGO stage and tumour metastasis, we only included FIGO stage and chemotherapy in the multivariate analysis (Table 3). FIGO stage was a significant predictor of progression-free survival (hazard ratio = 2.49, P = 0.048), whereas chemotherapy was not (hazard ratio = 1.47, P = 0.47). Univariate Cox regression analysis was also performed for overall survival; however, there was no significant relationship between any of the clinical variables investigated and overall survival.

Ultrasonographic features of primary and recurrent leiomyosarcoma lesions

Ultrasonography is the most widely used imaging examination for the screening and postoperative follow-up of patients with leiomyosarcoma. We found that ultrasonography could indicate the location of lesions before operation (Figure 2A and 2B). Additionally, 93.3% of the recurrences (14/15) were detected by ultrasonography, and only one patient experienced pulmonary relapse. Ultrasonography could clearly identify substantive masses in the pelvic cavity (Figures 2C). These observations imply that ultrasonography may serve as a comprehensive examination technique for recurrent pelvic leiomyosarcoma lesions.

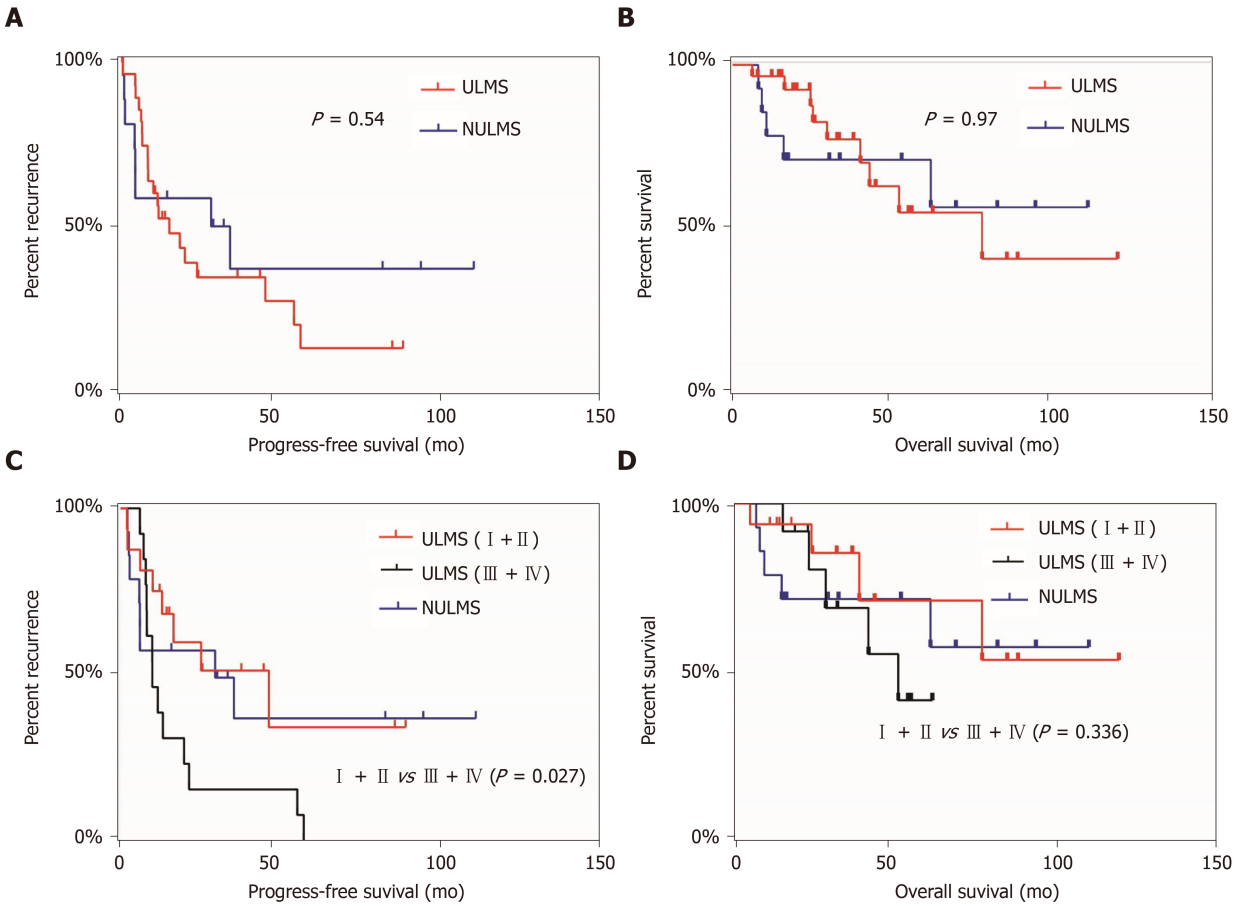

Figure 1 Survival curves of patients with uterine leiomyosarcoma and non-uterine leiomyosarcoma. A: Progression-free survival in uterine leiomyosarcoma and non-uterine leiomyosarcoma; B: Overall survival in uterine leiomyosarcoma and non-uterine leiomyosarcoma; C: Progression-free survival in stage I + II and stage III + IV uterine leiomyosarcoma and in non-uterine leiomyosarcoma; D: Overall survival in stage I + II and stage III + IV uterine leiomyosarcoma and in non-uterine leiomyosarcoma. ULMS: Uterine leiomyosarcoma; NULMS: Non-uterine leiomyosarcoma.

DISCUSSION

Although uterine leiomyosarcoma and non-uterine leiomyosarcoma are ostensibly the same disease, we gathered ample evidence implying the presence of significant differences in terms of clinical features, prognoses, and pathological characteristics. In our retrospective study, we assessed clinical aspects and prognoses of 35 and 16 patients with uterine leiomyosarcoma and non-uterine leiomyosarcoma, respectively, and summarised the ultrasonographic features of primary and recurrent tumour sites. We confirmed that patients with leiomyosarcoma do not necessarily exhibit elevated serum levels of known tumour biomarkers and that medical imaging is useful for identifying the presence of lesions but not their identities. Unlike in other gynaecological cancers[27], pelvic lymph node metastases were rarely observed in our leiomyosarcoma patients.

In terms of treatment, platinum-based chemotherapy accounted for the largest proportion of postoperative adjuvant therapies in both patients with uterine leiomyosarcoma and those with non-uterine leiomyosarcoma. The prognoses of our patients were poor, with no significant differences in progression-free survival and overall survival rates between the uterine leiomyosarcoma and non-uterine leiomyosarcoma groups. However, the univariate and multivariate analyses revealed that FIGO stage was significantly associated with progression-free survival. Because serum tumour biomarkers were found to be unreliable diagnostic features, imaging has a particularly important role for the diagnosis of leiomyosarcoma[28]. Ultrasonography was the most widely used modality, although its accuracy in diagnosing uterine leiomyosarcoma was unsatisfactory because most of such tumours were initially considered leiomyomas. In contrast to uterine leiomyosarcoma, most non-uterine leiomyosarcoma lesions were detected as pelvic masses by ultrasonography. In both uterine leiomyosarcoma and non-uterine leiomyosarcoma patients, however, ultrasonography accurately diagnosed relapse, demonstrating this technique's potential in monitoring leiomyosarcoma recurrence.

Table 3 Cox proportional hazards regression analysis of factors associated with progression-free survival

Factor	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	*P* value	Hazard ratio	95%CI	*P* value
Fage	0.98	0.94-1.01	0.25			
Primary site (uterine/non-uterine)	0.77	0.34-1.76	0.54			
FIGO stage						
III-IV/I-II	2.64	1.08-6.44	0.03	2.49	1.01-6.16	0.048
Non-uterine /I-II	1.20	0.45-3.23	0.71			
Non-uterine /III-IV	0.51	0.20-1.26	0.14			
Diameter of tumor (> 8 cm/≤ 8 cm)	2.65	0.81-8.68	0.11			
Myoma surgical history (yes/no)	1.60	0.73-3.53	0.24			
Surgery (laparotomy/laparoscopy)	1.11	0.90-1.33	0.87			
Ascites (increased/normal)	2.17	0.92-5.13	0.08			
Menopause (yes/no)	0.81	0.38-1.73	0.59			
Chemotherapy (yes/no)	2.95	1.13-7.70	0.03	1.47	0.52-4.22	0.47
CA125 (elevated/normal)	0.99	0.39-2.58	0.99			
Lymphadenectomy (yes/no)	1.36	0.63 -2.93	0.43			
Neoplasm metastasis (yes/no)	3.31	1.4 -7.82	0.006			

CI: Confidence interval.

While both uterine leiomyosarcoma and non-uterine leiomyosarcoma are sarcomas, they have varied anatomical locations, clinical characteristics, and gene expression patterns[29]. Our study also found that patients with these two types of leiomyosarcoma had different clinical symptoms because most patients with uterine leiomyosarcoma experienced menorrhagia and menstrual disorder, whereas those with non-uterine leiomyosarcoma more commonly presented with abdominal pain and distention. We found no significant differences in the prognoses of patients with uterine leiomyosarcoma and non-uterine leiomyosarcoma in terms of both progression-free survival and overall survival, consistent with the findings of Farid *et al*[29] but not with those of Lamm *et al*[4]. Such discrepancies can be attributed to the rare occurrence of leiomyosarcoma. Consistent with previous studies, we demonstrated that FIGO stage was the most significant factor associated with patient prognoses[12]. Chemotherapy may affect the prognosis of patients[30,31]. Moreover, we found that chemotherapy use was independently associated with poor progression-free survival in the univariate (but not multivariate) analysis.

The differential diagnosis of uterine leiomyoma and leiomyosarcoma remains a challenge in the medical imaging field. Ultrasonography is a reliable tool used to examine the uterus and accurately identify uterine leiomyomas[32]. Exacoustos *et al*[13] reported that uterine leiomyosarcoma lesions are significantly larger than uterine leiomyomas and have different grayscale sonographic characteristics. Furthermore, colour Doppler and power Doppler vascular patterns could be used as ancillary diagnostic methods to differentiate uterine sarcomas from other tumour types[32]. Our study has some limitations pertaining to its retrospective nature; therefore, prospective studies focusing on the medical imaging-based diagnosis of leiomyosarcoma are required, particularly those investigating the utility of power Doppler and contrast-enhanced ultrasonography.

In conclusion, our study suggests that serum tumour markers are of little value in leiomyosarcoma diagnosis, and ultrasonography cannot accurately differentiate leiomyosarcoma from uterine leiomyoma, although it remains valuable in monitoring recurrence. Our study also showed that FIGO stage is significantly associated with patient outcomes.

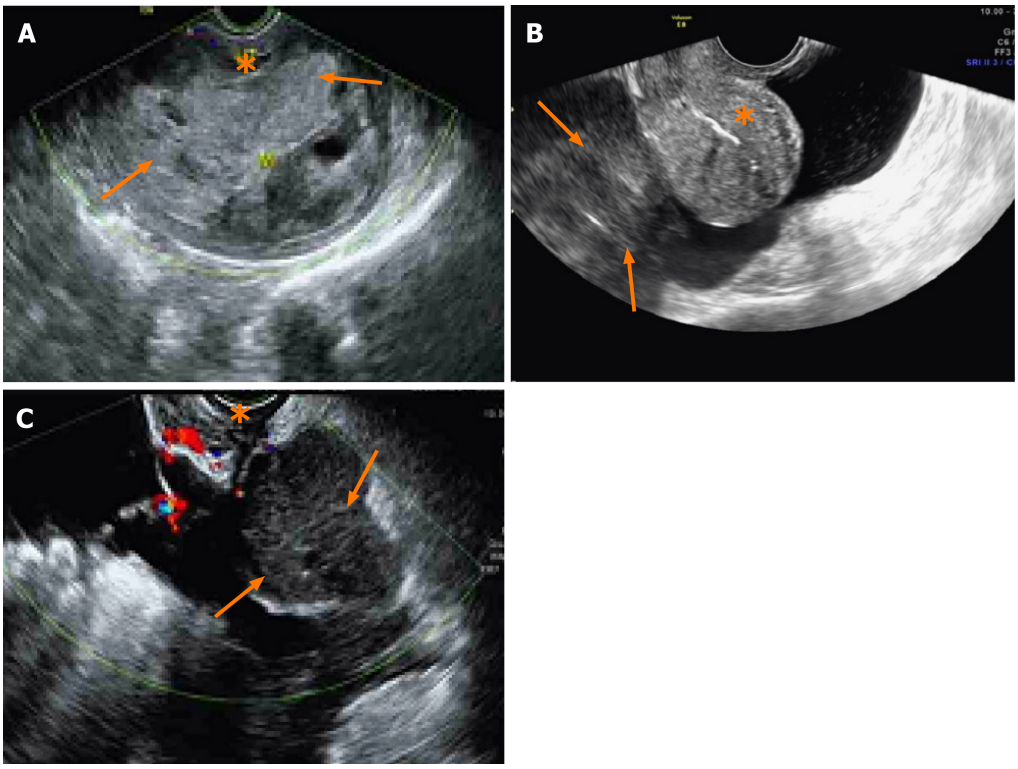

Figure 2 Ultrasound images of uterine leiomyosarcoma and non-uterine leiomyosarcoma. A: Ultrasound image of a preoperative patient with uterine leiomyosarcoma. Myometrium (asterisk) and intramural lesions of the uterus are shown (arrows); B: Ultrasound image of a preoperative patient with non-uterine leiomyosarcoma. Normal uterus (asterisk) and extrauterine lesions are shown (arrows); C: Ultrasound image of recurrent lesions in leiomyosarcoma. Normal vaginal stump (asterisk) and recurrent pelvic lesions are shown (arrows).

ARTICLE HIGHLIGHTS

Research background

Leimyosarcoma of the pelvic cavity heavily affects the health and life of women, but clinical characteristics and relevant diagnosis of the disease are still unclear. It is necessary to carry out clinical research related to pelvic leiomyosarcoma.

Research motivation

Preoperative diagnosis of pelvic leiomyosarcoma is very difficult, and only the pathological examination after operation can provide an accurate diagnosis for this disease. We would like to study the causes affecting diagnosis and factors affecting outcomes of those patients.

Research objectives

This study aimed to identify the outcomes and relevant perioperative evaluation of patients with pelvic leiomyosarcoma.

Research methods

We used Kaplan-Meier method to determine progression-free survival and overall survival rates. Univariate and multivariate Cox proportional hazards models were used to comprehensively analyse the prognostic factors

Research results

The results indicated that serum biomarkers had limited ability in leiomyosarcoma diagnosis and ultrasonography could not accurately differentiate leiomyosarcoma from uterine leiomyoma. However, most of the recurrent lesions could be detected using ultrasonography. FIGO stage was significantly associated with poor progression-free survival in the univariate and multivariate analyses.

Research conclusions

Serum tumour markers and ultrasonography cannot accurately diagnose pelvic leiomyosarcoma. Ultrasonography remains valuable in monitoring recurrence. FIGO stage is significantly associated with patient outcomes.

Research perspectives

Although accurate preoperative diagnosis of pelvic leiomyosarcoma was very difficult, our results showed that FIGO stage was significantly related to prognosis. Therefore, improving the

early diagnosis rate is a promising field in the future.

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