Ultrasound Obstet Gynecol 2019; **54**: 676–687
Published online 7 October 2019 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20270

Imaging in gynecological disease (15): clinical and ultrasound characteristics of uterine sarcoma

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KEYWORDS: endometrial stromal sarcoma; leiomyosarcoma; pattern recognition; sarcoma; ultrasonography

CONTRIBUTION

What are the novel findings of this work?
The study draws together multicenter experience of ultrasound findings in a large group of surgically confirmed uterine sarcomas and describes their characteristic features.

What are the clinical implications of this work?
Misclassifying a sarcoma as a benign myoma may result in no or delayed treatment or surgical treatment that is inappropriate, which would be highly likely to impact negatively on prognosis. Subjective assessment of ultrasound images based on the described features could help differentiate between benign and malignant myometrial tumors.

ABSTRACT

Objective *To describe the clinical and ultrasound characteristics of uterine sarcomas.*

Methods *This was a retrospective multicenter study. From the databases of 13 ultrasound centers, we identified patients with a histological diagnosis of uterine sarcoma with available ultrasound reports and ultrasound images who had undergone preoperative ultrasound examination between 1996 and 2016. As the first step, each author collected information from the original ultrasound reports from his/her own center on predefined ultrasound features of the tumors and by reviewing the ultrasound images to identify information on variables not described in the original report. As the second step, 16 ultrasound examiners reviewed the images electronically in a consensus meeting and described them using predetermined terminology.*

Results *We identified 116 patients with leiomyosarcoma, 48 with endometrial stromal sarcoma and 31 with undifferentiated endometrial sarcoma. Median age of the patients was 56 years (range, 26–86 years). Most patients were symptomatic at diagnosis (164/183 (89.6%)), the most frequent presenting symptom being abnormal*

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Accepted: 7 March 2019

vaginal bleeding (91/183 (49.7%)). Patients with endometrial stromal sarcoma were younger than those with leiomyosarcoma and undifferentiated endometrial sarcoma (median age, 46 years vs *57 and 60 years, respectively). According to the assessment by the original ultrasound examiners, the median diameter of the largest tumor was 91 mm (range, 7–321 mm). Visible normal myometrium was reported in 149/195 (76.4%) cases, and 80.0% (156/195) of lesions were solitary. Most sarcomas (155/195 (79.5%)) were solid masses (> 80% solid tissue), and most manifested inhomogeneous echogenicity of the solid tissue (151/195 (77.4%)); one sarcoma was multilocular without solid components. Cystic areas were described in 87/195 (44.6%) tumors and most cyst cavities had irregular walls (67/87 (77.0%)). Internal shadowing was observed in 42/192 (21.9%) sarcomas and fan-shaped shadowing in 4/192 (2.1%). Moderate or rich vascularization was found on color-Doppler examination in 127/187 (67.9%) cases. In 153/195 (78.5%) sarcomas, the original ultrasound examiner suspected malignancy. Though there were some differences, the results of the first and second steps of the analysis were broadly similar.*

Conclusions *Uterine sarcomas typically appear as solid masses with inhomogeneous echogenicity, sometimes with irregular cystic areas but only very occasionally with fan-shaped shadowing. Most are moderately or very well vascularized. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Aim

The aim of this retrospective study was to describe the clinical and ultrasound characteristics of uterine sarcomas.

Background

Epidemiology

Uterine sarcomas are rare malignant tumors arising from the mesenchymal tissues of the uterus, i.e. the endometrial stroma, uterine muscle and connective tissue. They represent 1% of female genital tract malignancies and 3–7% of all uterine malignances[1,2].

Population-based estimates of the incidence of uterine sarcoma range from 1.55 to 1.95 per 100 000 women per year[3]. It is estimated that 0.1–0.3% of patients operated on for presumed uterine leiomyoma have a uterine sarcoma[4–6].

According to the 2011 World Health Organization, uterine sarcomas are classified as leiomyosarcoma, endometrial stromal sarcoma or undifferentiated endometrial sarcoma[7], terminology that will be used in this report. Leiomyosarcoma has been reported to be the most common type of sarcoma, with an incidence of 41–60%, followed by carcinosarcoma (35%) and endometrial stromal sarcoma (16–20%)[8,9].

In published reports, the median age of women at diagnosis was 50–56 years for leiomyosarcoma, 40–55 years for endometrial stromal sarcoma and 55–60 years for undifferentiated stromal sarcoma[3,7,10], and the age-adjusted incidence of leiomyosarcoma was twice as high in black women as in white women[3,11]. Other risk factors for all histological types of sarcoma were advanced age and postmenopausal status[11]. Associations between endometrial stromal sarcoma and exposure to tamoxifen, unopposed estrogen and polycystic ovary syndrome have been reported[3,12–14]. Endometrial stromal sarcoma is more common in women with a history of pelvic radiation[7].

Microscopy

Histopathological diagnosis of uterine sarcomas has always been a challenge, because many benign variants of smooth-muscle tumors (e.g. mitotically active leiomyomas, apoplectic leiomyomas and leiomyomas with bizarre nuclei) can simulate leiomyosarcomas. Diagnosis of endometrial stromal sarcoma is also difficult, which is reflected by frequent changes in their classification[15].

The histopathological diagnosis of uterine leiomyosarcoma is based on a mitotic count exceeding 10 mitotic figures per 10 high-power-fields (MF/10 HPF), cellular atypia and the presence of coagulative necrosis[16,17]. Leiomyosarcomas are composed of fascicles of spindle cells with abundant eosinophilic cytoplasm[7]. Cellular pleomorphism can be marked in poorly differentiated neoplasms. The mitotic index is usually high[18,19]. Tumor-cell necrosis occurs in one third of leiomyosarcomas and is characterized by an abrupt transition from viable to non-viable tissue. Both cytological atypia and mitotic activity should usually be present to diagnose leiomyosarcoma because of the difficulty in distinguishing reliably between necrosis due to infarction and tumor-cell necrosis[19–21]. Vascular invasion is found in 10–22% of leiomyosarcomas, and many invade the surrounding myometrium[7]. Several immunohistochemical and molecular genetic studies on uterine leiomyosarcomas have been published[19,22–27]. In 30–40% of leiomyosarcomas, estrogen, progesterone and androgen receptors are found[19,24].

The term endometrial stromal sarcoma is applied to neoplasms composed of cells that resemble endometrial stromal cells of the proliferative endometrium[19]. Endometrial stromal sarcomas are low-grade tumors with cells of relatively uniform size and shape. They typically show < 3 MF/10 HPF, but can also have greater mitotic activity[7]. Proliferation of small vessels and arterioles resembling endometrial spiral arterioles is a characteristic finding. Cluster of differentiation-10 (CD-10), a metalloproteinase, is the most specific biomarker of endometrial stromal sarcoma[27].

In undifferentiated endometrial sarcomas, tumor-cell necrosis is generally present and can be extensive. Mitotic activity is variable but there are usually > 10 MF/10 HPF[1]. These tumors should be diagnosed only after extensive

sampling has excluded smooth-muscle or skeletal-muscle differentiation or small foci of carcinoma, because findings of these would result in a diagnosis of carcinosarcoma. Undifferentiated endometrial sarcomas lack immunoreaction for estrogen and progesterone receptors, but many are immunoreactive for endothelial growth factor receptor[28]. CD-10 expression is not helpful in the differential diagnosis from other uterine sarcomas, because undifferentiated endometrial sarcomas as well as leiomyosarcomas and carcinosarcomas may express this marker.

Macroscopy

Leiomyosarcomas are on average 6–9 cm in diameter and the cut surface is typically soft, bulging, fleshy, necrotic and hemorrhagic, with irregular margins[19]. Infiltrative growth into the myometrium is often noted grossly (or under the microscope), but some leiomyosarcomas may be relatively well circumscribed. About two-thirds are intramural, one-fifth submucosal and one-tenth subserosal[19]. They are often single masses (50–75% of cases)[7]. If a leiomyosarcoma is associated with leiomyoma, the sarcoma is usually the largest mass[19]. Leiomyosarcomas tend to be larger and softer than leiomyomas[7,29].

Endometrial stromal sarcomas have irregular nodular growth involving the endometrium, myometrium or both. Size is variable but most range from 5 to 10 cm. They typically have a yellow to tan colored fleshy cut surface with hemorrhage and necrosis occasionally seen[19].

Undifferentiated endometrial sarcomas grow as soft polypoid tumors that bulge into the endometrial cavity and invade the underlying myometrium. Hemorrhage and necrosis are frequently present[19].

Clinical features and prognosis

Women with leiomyosarcoma often present with symptoms of abnormal uterine bleeding (56%) either in the pre- or postmenopausal period, a palpable pelvic mass (54%) or abdominal pain (22%)[1]. Signs and symptoms resemble those of benign leiomyomas, and preoperative distinction between the two on the basis of clinical information may be difficult. Malignancy should be suspected in cases of tumor growth in postmenopausal women who are not on hormone replacement therapy[30]. Occasionally, the presenting symptoms are explained by tumor rupture (hemoperitoneum), extrauterine growth (in one-third to one-half of cases) or metastases[19]. Leiomyosarcomas are very aggressive tumors with a poor prognosis[19]. Treatment includes total abdominal hysterectomy and debulking of the tumor outside the uterus. Oophorectomy is generally recommended, but it might not be necessary in patients of reproductive age with early-stage disease. However, even in such patients, oophorectomy must be considered if the tumor is estrogen-/progesterone-receptor positive. Lymph-node dissection is controversial, but, if there are no signs of metastatic lymph nodes, the procedure can be avoided[31–33]. The role of adjuvant radiation therapy for patients with Stage I/II leiomyosarcoma is highly contentious, because it does not seem to affect either progression or survival[34,35]. The benefits of chemotherapy for patients who have undergone complete resection of disease limited to the uterus are also controversial[36]. Occasionally, estrogen receptor-positive tumors will respond to hormonal treatment, for example with progestin, aromatase inhibitor, gonadotropin-releasing hormone (GnRH) analogs or GnRH analogs plus megestrol acetate[37].

Patients with endometrial stromal sarcoma often present with abnormal uterine bleeding and/or pelvic pain, but as many as 25% may be asymptomatic[38]. Endometrial stromal sarcomas are indolent tumors with a favorable prognosis, stage being the most important prognostic factor. The 5-year disease-specific survival rate for Stages I and II tumors is 90%, compared with 50% for Stages III and IV tumors[39,40]. The surgical treatment of endometrial stromal sarcoma is hysterectomy and bilateral salpingo-oophorectomy[41]. However, in young patients affected by early-stage endometrial stromal sarcoma who wish to preserve reproductive function, fertility-sparing surgery (hysteroscopic removal of the lesion and sparing of the uterus and ovaries) is an option[42,43]. Endometrial stromal sarcomas are usually hormone receptor-positive, and progestins and aromatase inhibitors are used as adjuvant treatment in these cases[27].

Undifferentiated endometrial sarcomas have a very poor prognosis, and most patients die of the disease within 2 years after diagnosis[19]. Treatment is primarily surgical with or without adjuvant radiotherapy or chemotherapy[44,45].

METHODS

This was a retrospective study of women diagnosed with uterine sarcoma between 1996 and 2016. From the databases of 13 ultrasound centers, we identified patients with a histological diagnosis of uterine sarcoma. We included only women who had undergone preoperative ultrasound examination by an experienced ultrasound examiner, with ultrasound reports and images available for analysis. All women underwent transvaginal or transrectal ultrasound examination supplemented with a transabdominal scan if necessary to allow comprehensive examination of the uterus and adnexa. For most ultrasound examinations, high-end ultrasound equipment with a 5.0–9.0-MHz vaginal probe or 3.5–5.0-MHz abdominal probe was used.

Information on the patients' age, presenting symptoms, menopausal status, parity, previous exposure to pelvic radiation and International Federation of Gynecology and Obstetrics (FIGO) stage of the sarcoma was retrieved retrospectively from patient records and entered into a dedicated Excel file (Microsoft Office Excel 2011; Redmond, WA, USA). Postmenopausal was defined as absence of vaginal bleeding for at least 1 year after the age of 40 years, provided that the amenorrhea could not be explained by medication or disease.

As the first step, information on the gray-scale and color-Doppler ultrasound features of the sarcomas was obtained as follows: each author collected information from the original ultrasound reports on predefined ultrasound features of the tumors from his/her own center, and by checking saved ultrasound images and videoclips to identify information on features not described in the original reports. The following ultrasound information was recorded in the Excel file: the largest diameter of the largest uterine lesion suspected to be a sarcoma, visible normal myometrium (yes, no), echogenicity of the solid tissue of the tumor as assessed subjectively (homogeneous *vs* inhomogeneous), presence of cystic areas within the tumor, regularity of the outline of cyst cavities (defining it as irregular if at least one cyst cavity had irregular contours), echogenicity of cyst content (anechoic, low level, hemorrhagic, ground glass or other)[46], type of tumor (unilocular, unilocular-solid, multilocular, multilocular-solid or solid)[46], presence of shadows, described as either 'fan-shaped shadowing' (as seen in adenomyosis) or 'internal shadows' (as often seen in leiomyomas)[47], calcifications (defined as hyperechoic foci with shadowing behind), regularity of the tumor border (regular or irregular), endometrial cavity visible (yes, no or no reliable information), free fluid in the pouch of Douglas and ascites (defined as fluid outside the pouch of Douglas). The presence of additional lesions typical of benign leiomyomas was also noted[47]. To assess the vascularization of the tumor, the color content of the tumor on color-Doppler ultrasound examination was estimated and classified using a color score. A color score of 1 means that no color- or power-Doppler signals were detected in the tumor; a score of 2 that a minimal amount of color-Doppler signal was detected; a color score of 3 that a moderate amount was detected; and a score of 4 that abundant signal was detected[46]. The diagnosis suggested by the original ultrasound examiner in their original report was also recorded, as was information on whether the lesion was judged to manifest ultrasound features typical of a benign myoma. Ultrasound variables were assigned the answer 'no reliable information' when they were neither described in the original report nor deducible from digital images or videoclips.

As the second step, a consensus meeting was held with 16 ultrasound examiners from gynecological referral ultrasound units from four countries, all of whom had more than 10 years' experience in gynecological ultrasonography. The aim of the meeting was to try to identify typical ultrasound patterns of sarcomas. The consensus meeting started with the organizers of the meeting (M.L. and A.C.T.) proposing which ultrasound variables (for example 'shadowing' or 'echogenicity of solid tissue') should be used to describe uterine sarcomas, and showing representative images of the different categories of each variable. After discussion among the participants, 11 variables (with definitions of each variable category) were selected for use in the second analysis of the images (Figure S1). Most of the variables and variable categories were the same as those used in the first step of the analysis: visible normal myometrium; echogenicity of the solid tissue of the mass; presence of cystic areas; regularity of internal cyst walls; shadowing; calcifications; regularity of tumor border; and appearance consistent with typical benign myoma[47]. The color score was assessed separately for circumferential and intralesional vascularization[47]. Classification of the echogenicity of the cystic content differed from that in the first step of analysis: anechoic, low level, hemorrhagic, ground glass and mixed (more than one type of cystic content in the same cyst cavity; for example fluids of different density). In case of multiple-cyst locules with different cystic content, the predominant type of cystic content was reported, while echogenicity was classified as 'variable' when no one type of cystic content dominated over the other(s). A new variable describing the echogenicity of the solid tissue of the tumor was introduced: the 'cooked appearance'. It indicates a lack of structure of the solid tissue of the tumor (Figure 1). After having agreed on the variables and terminology, the 16 ultrasound examiners looked at representative electronic ultrasound images of each

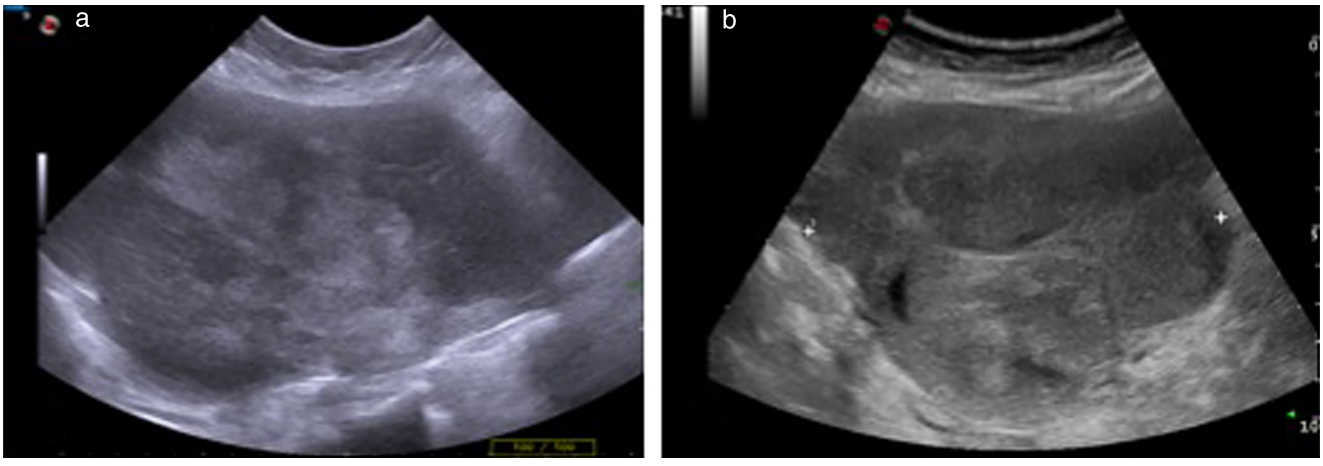

Figure 1 Ultrasound images of leiomyosarcoma (a) and undifferentiated endometrial sarcoma (b), showing 'cooked appearance' of solid tissue, i.e. lack of structure of solid tissue of tumor and absence of shadowing.

tumor and described them using the predefined variables (Figure S1). Each observer noted his/her evaluation on a dedicated research form. A variable was assigned the answer 'impossible to say' when the examiner was unable to make a decision, and as 'not assessable' when the available ultrasound images did not contain the information necessary to provide an answer. All data were entered into a dedicated Excel file (Microsoft Office).

Statistical calculations were performed using SPSS software PASW version 20.0 (IBM Corp., New York, NY, USA). Results are presented for all sarcomas as well as separately for leiomyosarcoma, endometrial stromal sarcoma and undifferentiated endometrial sarcoma. Results based on the original ultrasound reports and retrospective evaluation of ultrasound images by the principal investigators at each center (referred to here as 'results obtained by original examiner') are presented as median (range) or absolute frequency (percentage). The results of the consensus meeting are presented as the prevalence of a variable category, calculated as the percentage of times that the category was noted relative to the total number of ratings for that variable.

RESULTS

We identified 195 patients with a uterine sarcoma from the database of the contributing ultrasound centers, including 116 leiomyosarcomas, 48 endometrial stromal sarcomas and 31 undifferentiated endometrial sarcomas. The number of cases contributed by each center is shown after the main text.

Demographic background data and FIGO stage of the tumors are shown in Table 1. Median age of the patients was 56 years (range, 26–86 years) and most were postmenopausal (111/195 (56.9%)). The majority of patients were symptomatic at diagnosis (164/183 (89.6%)), and the most frequent presenting symptom was abnormal vaginal bleeding (91/183 (49.7%)). Most tumors were FIGO Stage I (120/188 (63.8%)). Patients with endometrial stromal sarcoma were younger than those with leiomyosarcoma and undifferentiated endometrial sarcoma (median age 46 *vs* 57 and 60 years, respectively) and they were more often premenopausal (32/48 (66.7%) *vs* 47/116 (40.5%) and 5/31 (16.1%), respectively). Abnormal vaginal bleeding was more common in patients with endometrial stromal sarcoma and undifferentiated endometrial sarcoma than in those with leiomyosarcoma (28/46 (60.9%) and 21/30 (70.0%) *vs* 42/107 (39.3%), respectively). Endometrial stromal sarcomas were more often FIGO Stage I than were leiomyosarcomas and undifferentiated endometrial sarcomas (39/48 (81.3%) *vs* 65/110 (59.1%) and 16/30 (53.3%), respectively), while undifferentiated endometrial sarcomas were more often FIGO Stage IV than were leiomyosarcomas and endometrial stromal sarcomas (9/30 (30.0%) *vs* 21/110 (19.1%) and 4/48 (8.3%), respectively).

The sonographic characteristics of the uterine sarcomas are shown in Table 2 and in Figures 2–5. Median diameter of the largest tumor was 91 mm (range, 7–321 mm). According to the assessment by the original examiners (first step of the analysis), all but one sarcoma with reliable information on sonographic tumor type ($n = 172$) contained solid components, and the vast majority were solid tumors (155/172 (90.1%)). Most sarcomas (151/195 (77.4%)) manifested inhomogeneous echogenicity of the solid tissue, and cystic areas were described in 87/195 (44.6%), most of which had irregular walls

Table 1 Clinical characteristics of 195 patients with uterine sarcoma, overall and according to type of sarcoma

		Type of tumor		
Characteristic	*All (n = 195)*	*Leiomyosarcoma (n = 116)*	*Endometrial stromal sarcoma (n = 48)*	*Undifferentiated endometrial sarcoma (n = 31)*
Age at diagnosis (years)	56 (26–86)	57 (30–86)	46 (26–79)	60 (28–84)
Nulliparous	50 (25.6)	27 (23.3)	15 (31.3)	8 (25.8)
Premenopausal	84 (43.1)	47 (40.5)	32 (66.7)	5 (16.1)
Current hormonal therapy*	26/185 (14.1)	16/109 (14.7)	5/47 (10.6)	5/29 (17.2)
Previous pelvic radiation†	1/186 (0.5)	1/109 (0.9)	0/48 (0.0)	0/29 (0.0)
Symptoms‡				
Asymptomatic	19/183 (10.4)	12/107 (11.2)	5/46 (10.9)	2/30 (6.7)
Abnormal vaginal bleeding	91/183 (49.7)	42/107 (39.3)	28/46 (60.9)	21/30 (70.0)
Abdominal pain	30/183 (16.4)	19/107 (17.8)	8/46 (17.4)	3/30 (10.0)
Abdominal distension	15/183 (8.2)	13/107 (12.1)	0/46 (0.0)	2/30 (6.7)
Mass detected on other imaging technique	7/183 (3.8)	3/107 (2.8)	2/46 (4.3)	2/30 (6.7)
Self-palpated mass	3/183 (1.6)	3/107 (2.8)	0/46 (0.0)	0/30 (0.0)
More than one of above symptoms	14/183 (7.7)	11/107 (10.3)	3/46 (6.5)	0/30 (0.0)
Other	4/183 (2.2)	4/107 (3.7)	0/46 (0.0)	0/30 (0.0)
FIGO stage§				
I	120/188 (63.8)	65/110 (59.1)	39/48 (81.3)	16/30 (53.3)
II	12/188 (6.4)	7/110 (6.4)	3/48 (6.3)	2/30 (6.7)
III	22/188 (11.7)	17/110 (15.5)	2/48 (4.2)	3/30 (10.0)
IV	34/188 (18.1)	21/110 (19.1)	4/48 (8.3)	9/30 (30.0)

Data are given as median (range), *n* (%) or *n/N* (%). Data available for: *185 cases; †186 cases; ‡183 cases; §188 cases.

Table 2 Ultrasound characteristics of uterine sarcomas in original ultrasound examiner's report and prevalence of ultrasound characteristics when images were reviewed by 16 experienced ultrasound examiners in consensus meeting, overall and according to type of sarcoma

			Type of tumor					
	All		*Leiomyosarcoma*		*Endometrial stromal sarcoma*		*Undifferentiated endometrial sarcoma*	
Characteristic	*Original examiner (n = 195)*	*Consensus meeting* (n = 152) (Total ratings, 2110)*	*Original examiner (n = 116)*	*Consensus meeting* (n = 92) (Total ratings, 1284)*	*Original examiner (n = 48)*	*Consensus meeting* (n = 33) (Total ratings, 454)*	*Original examiner (n = 31)*	*Consensus meeting* (n = 27) (Total ratings, 372)*
Modality of scan								
Transvaginal	93 (47.7)	—	46 (39.7)	—	33 (68.8)	—	14 (45.2)	—
Transvaginal and transabdominal	100 (51.3)	—	69 (59.5)	—	15 (31.3)	—	16 (51.6)	—
Transrectal and transabdominal	2 (1.0)	—	1 (0.9)	—	0 (0.0)	—	1 (3.2)	—
Largest diameter of lesion (mm)	91 (7–321)	—	106 (30–321)	—	68 (12–210)	—	70 (7–250)	—
Visible normal myometrium								
Yes	149 (76.4)	1128 (53.5)	81 (69.8)	599 (46.7)	44 (91.7)	299 (65.9)	24 (77.4)	230 (61.8)
No	46 (23.6)	809 (38.3)	35 (30.2)	577 (44.9)	4 (8.3)	128 (28.2)	7 (22.6)	104 (28.0)
Impossible to say	—	136 (6.4)	—	83 (6.5)	—	22 (4.8)	—	31 (8.3)
Not assessable	—	37 (1.8)	—	25 (1.9)	—	5 (1.1)	—	7 (1.9)
Type of tumor								
Multilocular	1 (0.5)	—	0 (0.0)	—	0 (0.0)	—	1 (3.2)	—
Multilocular-solid	16 (8.2)	—	12 (10.3)	—	3 (6.3)	—	1 (3.2)	—
Solid	155 (79.5)	—	85 (73.3)	—	43 (89.6)	—	27 (87.1)	—
No (reliable) information	23 (11.8)	—	19 (16.4)	—	2 (4.2)	—	2 (6.5)	—
Echogenicity of solid tissue								
Homogeneous	43 (22.1)	158 (7.5)	22 (19.0)	68 (5.3)	14 (29.2)	42 (9.3)	7 (22.6)	48 (12.9)
Inhomogeneous	151 (77.4)	1925 (91.2)	94 (81.0)	1211 (94.3)	34 (70.8)	406 (89.4)	23 (74.2)	308 (82.8)
Impossible to say	—	16 (0.8)	—	2 (0.2)	—	2 (0.4)	—	12 (3.2)
Not assessable (no solid tissue)	1 (0.5)	11 (0.5)	0 (0.0)	3 (0.2)	0 (0.0)	4 (0.9)	1 (3.2)	4 (1.1)
Cystic areas								
Yes	87 (44.6)	1155 (54.7)	54 (46.6)	746 (58.1)	18 (37.5)	239 (52.6)	15 (48.4)	170 (45.7)
No	108 (55.4)	902 (42.7)	62 (53.4)	512 (39.9)	30 (62.5)	208 (45.8)	16 (51.6)	182 (48.9)
Impossible to say	—	37 (1.8)	—	18 (1.4)	—	4 (0.9)	—	15 (4.0)
Not assessable	—	16 (0.8)	—	8 (0.6)	—	3 (0.7)	—	5 (1.3)
Cystic area of walls if cystic areas present								
Regular	20/87 (23.0)	202/1155 (17.5)	10/54 (18.5)	133/746 (17.8)	7/18 (38.9)	40/239 (16.7)	3/15 (20.0)	29/170 (17.1)
Irregular	67/87 (77.0)	935/1155 (81.0)	44/54 (81.5)	602/746 (80.7)	11/18 (61.1)	194/239 (81.2)	12/15 (80.0)	139/170 (81.8)
Impossible to say	—	16/1155 (1.4)	—	11/746 (1.5)	—	3/239 (1.3)	—	2/170 (1.2)
Not assessable	—	2/1155 (0.2)	—	0 (0.0)	—	2/239 (0.8)	—	0 (0.0)
Echogenicity of cystic content								
Anechoic	43/87 (49.4)	484/1155 (41.9)	26/54 (48.1)	305/746 (40.9)	9/18 (50.0)	117/239 (49.0)	8/15 (53.3)	62/170 (36.5)
Low level	23/87 (26.4)	255/1155 (22.1)	18/54 (33.3)	150/746 (20.1)	4/18 (22.2)	52/239 (21.8)	1/15 (6.7)	53/170 (31.2)
Hemorrhagic	9/87 (10.3)	27/1155 (2.3)	4/54 (7.4)	20/746 (2.7)	2/18 (11.1)	6/239 (2.5)	3/15 (20.0)	1/170 (0.6)
Ground glass	11/87 (12.6)	95/1155 (8.2)	6/54 (11.1)	67/746 (9.0)	2/18 (11.1)	11/239 (4.6)	3/15 (20.0)	17/170 (10.0)
Other	1/87 (1.1)	—	0 (0.0)	—	1/18 (5.6)	—	0 (0.0)	—
Mixed	—	122/1155 (10.6)	—	83/746 (11.1)	—	19/239 (7.9)	—	20/170 (11.8)
Variable	—	163/1155 (14.1)	—	115/746 (15.4)	—	32/239 (13.4)	—	16/170 (9.4)
Impossible to say	—	7/1155 (0.6)	—	5/746 (0.7)	—	1/239 (0.4)	—	1/170 (0.6)
Not assessable	—	2/1155 (0.2)	—	1/746 (0.1)	—	1/239 (0.4)	—	0 (0.0)
Shadowing								
No shadowing	146 (74.9)	1306 (61.9)	82 (70.7)	746 (58.1)	37 (77.1)	276 (60.8)	27 (87.1)	284 (76.3)
Internal shadows	42 (21.5)	517 (24.5)	32 (27.6)	371 (28.9)	8 (16.7)	100 (22.0)	2 (6.5)	46 (12.4)
Fan-shaped shadowing	4 (2.1)	247 (11.7)	1 (0.9)	152 (11.8)	2 (4.2)	69 (15.2)	1 (3.2)	26 (7.0)
No (reliable) information	3 (1.5)	—	1 (0.9)	—	1 (2.1)	—	1 (3.2)	—
Impossible to say	—	24 (1.1)	—	11 (0.9)	—	2 (0.4)	—	11 (3.0)
Not assessable	—	16 (0.8)	—	4 (0.3)	—	7 (1.5)	—	5 (1.3)
Calcification								
Yes	18 (9.2)	172 (8.2)	12 (10.3)	116 (9.0)	4 (8.3)	30 (6.6)	2 (6.5)	26 (7.0)
No	163 (83.6)	1907 (90.4)	97 (83.6)	1157 (90.1)	40 (83.3)	418 (92.1)	26 (83.9)	332 (89.2)
No (reliable) information	14 (7.2)	—	7 (6.0)	—	4 (8.3)	—	3 (9.7)	
Impossible to say	—	18 (0.9)	—	7 (0.5)	—	2 (0.4)	—	9 (2.4)
Not assessable	—	13 (0.6)	—	4 (0.3)	—	4 (0.9)	—	5 (1.3)

Continued over.

Table 2 *Continued*

Characteristic	All		Type of tumor					
			Leiomyosarcoma		Endometrial stromal sarcoma		Undifferentiated endometrial sarcoma	
	Original examiner (n = 195)	Consensus meeting* (n = 152) (Total ratings, 2110)	Original examiner (n = 116)	Consensus meeting* (n = 92) (Total ratings, 1284)	Original examiner (n = 48)	Consensus meeting* (n = 33) (Total ratings, 454)	Original examiner (n = 31)	Consensus meeting* (n = 27) (Total ratings, 372)
Tumor border								
Regular	91 (46.7)	685 (32.5)	55 (47.4)	411 (32.0)	29 (60.4)	173 (38.1)	7/31 (22.6)	101 (27.2)
Irregular	103 (52.8)	1310 (62.1)	61 (52.6)	807 (62.9)	19 (39.6)	265 (58.4)	23/31 (74.2)	238 (64.0)
Impossible to say	1 (0.5)	95 (4.5)	0 (0.0)	57 (4.4)	0 (0.0)	8 (1.8)	1/31 (3.2)	30 (8.1)
Not assessable	—	20 (0.9)	—	9 (0.7)	—	8 (1.8)	—	3 (0.8)
Cooked appearance								
Yes	—	457 (21.7)	—	317 (24.7)	—	62 (13.7)	—	78 (21.0)
No	—	1221 (57.9)	—	709 (55.2)	—	316 (69.6)	—	196 (52.7)
Impossible to say	—	373 (17.7)	—	226 (17.6)	—	57 (12.6)	—	90 (24.2)
Not assessable	—	59 (2.8)	—	32 (2.5)	—	19 (4.2)	—	8 (2.2)
Color score								
1	6 (3.1)	—	5 (4.3)	—	1 (2.1)	—	0 (0.0)	—
2	54 (27.7)	—	27 (23.3)	—	19 (39.6)	—	8 (25.8)	—
3	73 (37.4)	—	45 (38.8)	—	16 (33.3)	—	12 (38.7)	—
4	54 (27.7)	—	34 (29.3)	—	11 (22.9)	—	9 (29.0)	—
No (reliable) information	8 (4.1)	—	5 (4.3)	—	1 (2.1)	—	2 (6.5)	—
Circumferential color score								
1/2 (absent or minimal)	—	820 (38.9)	—	498 (38.8)	—	181 (39.9)	—	141 (37.9)
3/4 (moderate or abundant)	—	834 (39.5)	—	524 (40.8)	—	209 (46.0)	—	101 (27.2)
Impossible to say	—	97 (4.6)	—	53 (4.1)	—	12 (2.6)	—	32 (8.6)
Not assessable	—	359 (17.0)	—	209 (16.3)	—	52 (11.5)	—	98 (26.3)
Internal color score								
1/2 (absent or minimal)	—	728 (34.5)	—	456 (35.5)	—	169 (37.2)	—	103 (27.7)
3/4 (moderate or abundant)	—	1117 (52.9)	—	707 (55.1)	—	239 (52.6)	—	171 (46.0)
Impossible to say	—	26 (1.2)	—	11 (0.9)	—	0 (0.0)	—	15 (4.0)
Not assessable	—	239 (11.3)	—	110 (8.6)	—	46 (10.1)	—	83 (22.3)
Lesion typical of benign myoma								
Yes	28 (14.4)	178 (8.4)	18 (15.5)	106 (8.3)	9 (18.8)	50 (11.0)	1 (3.2)	22 (5.9)
No	167 (85.6)	1833 (86.9)	98 (84.5)	1117 (87.0)	39 (81.3)	385 (84.8)	30 (96.8)	331 (89.0)
Impossible to say	—	89 (4.2)	—	58 (4.5)	—	16 (3.5)	—	15 (4.0)
Not assessable	—	10 (0.5)	—	3 (0.2)	—	3 (0.7)	—	4 (1.1)
Endometrial cavity								
Clearly visualized	93 (47.7)	—	54 (46.6)	—	27 (56.3)	—	12 (38.7)	—
Not clearly visualized	99 (50.8)	—	59 (50.9)	—	21 (43.8)	—	19 (61.3)	—
No reliable information	3 (1.5)	—	3 (2.6)	—	0 (0.0)	—	0 (0.0)	—
Ultrasound signs of other lesions typical of benign myoma								
Yes	39 (20.0)	—	22 (19.0)	—	13 (27.1)	—	4 (12.9)	
No	156 (80.0)	—	94 (81.0)	—	35 (72.9)	—	27 (87.1)	—
Free fluid in pouch of Douglas								
Yes	13 (6.7)	—	8 (6.9)	—	2 (4.2)	—	3 (9.7)	—
No	182 (93.3)	—	108 (93.1)	—	46 (95.8)	—	28 (90.3)	—
Ascites								
Yes	4 (2.1)	—	3 (2.6)	—	1 (2.1)	—	0 (0.0)	—
No	191 (97.9)	—	113 (97.4)	—	47 (97.9)	—	31 (100.0)	—
Diagnosis on subjective assessment								
Clearly malignant	92 (47.2)	—	60 (51.7)	—	11 (22.9)	—	21 (67.7)	—
Malignancy could not be excluded	61 (31.3)	—	30 (25.9)	—	23 (47.9)	—	8 (25.8)	—
Benign	40 (20.5)	—	26 (22.4)	—	13 (27.1)	—	1 (3.2)	—
No reliable information	2 (1.0)	—	0 (0.0)	—	1 (2.1)	—	1 (3.2)	—

Results are presented as median (range), *n* (%) or *n*/*N* (%). *Overall prevalence of category calculated as percentage of times category was noted by examiners relative to total number of ratings calculated as follows. For 'All' group, 10 patients × 16 raters = 160; 114 patients × 14 raters = 1596; 23 patients × 13 raters = 299; 5 patients × 11 raters = 55; total ratings = 2110. For leiomyosarcoma group, 10 patients × 16 raters = 160; 64 patients × 14 raters = 896; 15 patients × 13 raters = 195; 3 patients × 11 raters = 33; total ratings = 1284. For endometrial stromal sarcoma group, 29 patients × 14 raters = 406; 2 patients × 13 raters = 26; 2 patients × 11 raters = 22; total ratings = 454. For undifferentiated endometrial sarcoma cases, 21 patients × 14 raters = 294; 6 patients × 13 raters = 78; total ratings = 372.

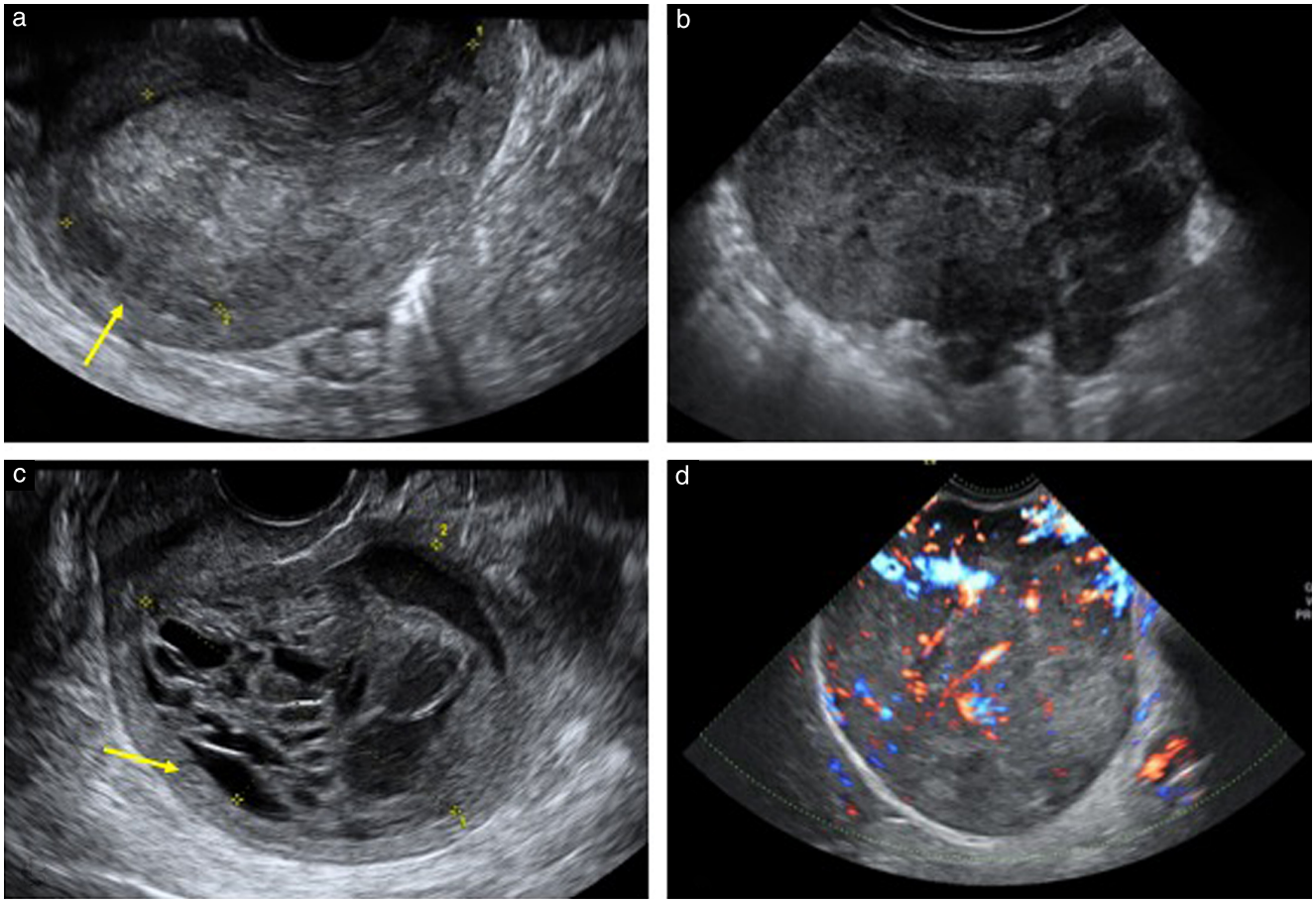

Figure 2 Ultrasound images of uterine sarcomas. According to assessment by original examiner, there was normal visible myometrium (yellow arrows) in 149/195 (76.4%) cases (a,c), 151/195 (77.4%) sarcomas manifested inhomogeneous echogenicity of solid tissue (a,b,d), 87/195 (44.6%) contained cystic areas (c), 103/195 (52.8%) had irregular tumor borders (b) and 127/187 (67.9%) manifested moderate or rich vascularization (d).

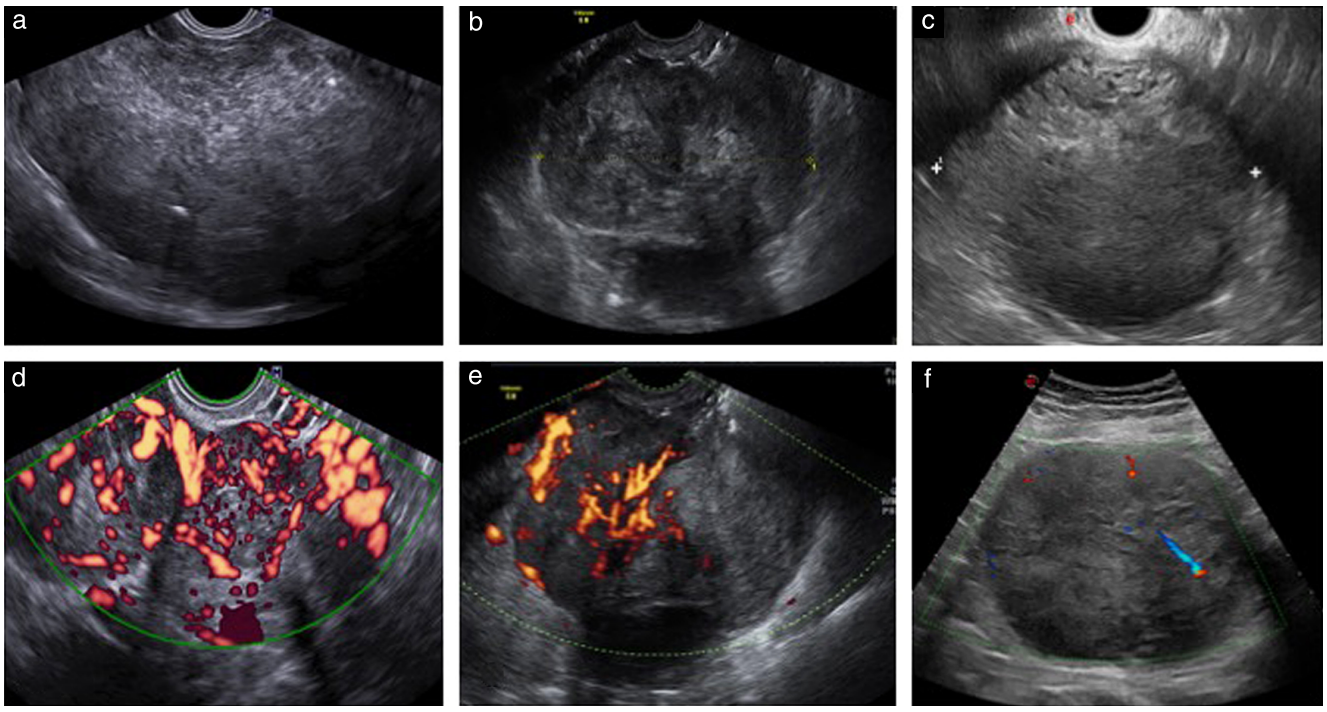

Figure 3 Grayscale ultrasound images of three leiomyosarcomas (a–c) and corresponding color- or power-Doppler images showing rich (d), moderate (e) and minimal (f) vascularization.

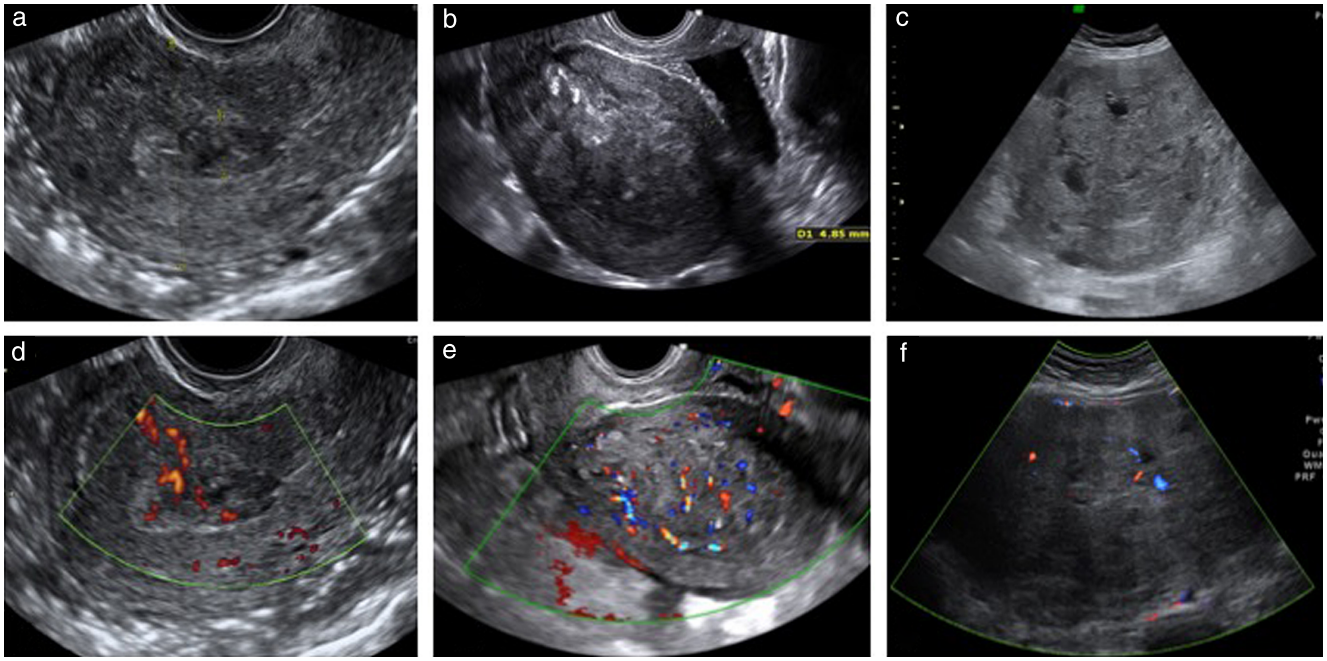

Figure 4 Grayscale ultrasound images of three endometrial stromal sarcomas (a–c) and corresponding color- or power-Doppler images showing moderate (d,e) and minimal (f) vascularization.

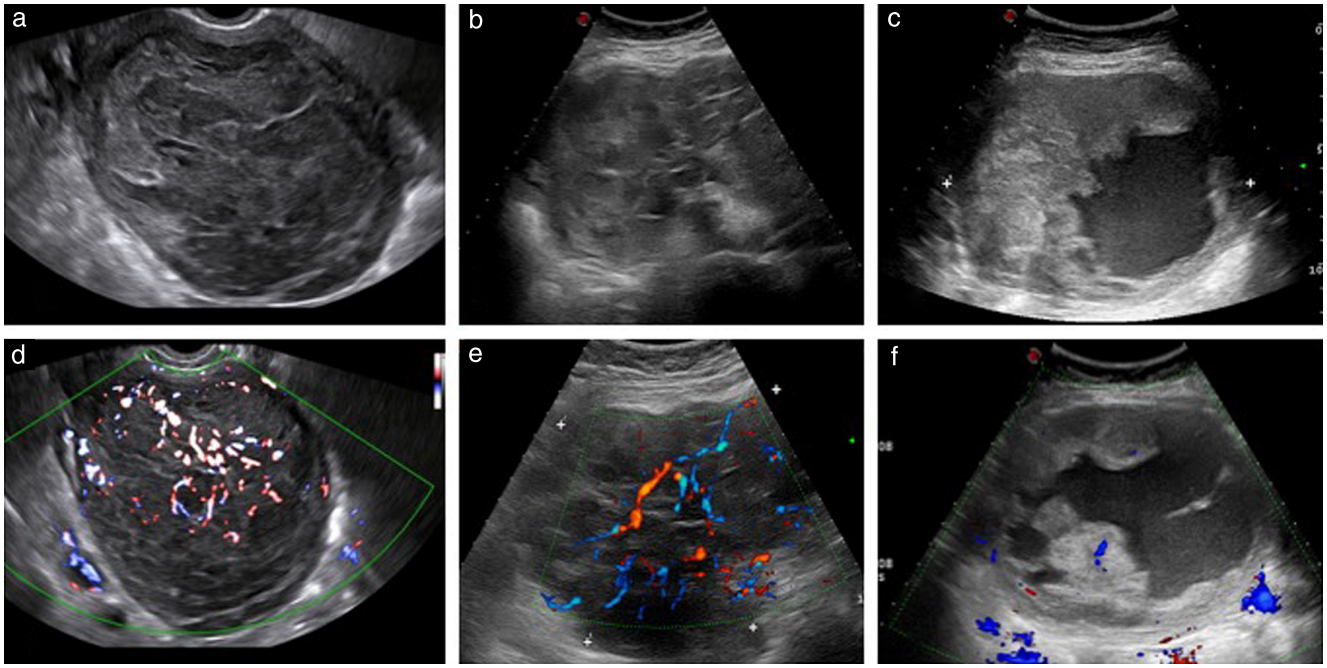

Figure 5 Grayscale ultrasound images of three undifferentiated endometrial sarcomas (a–c) and corresponding color- or power-Doppler images showing rich (d,e) and minimal (f) vascularization.

(67/87 (77.0%)). Internal shadows were found in 42/192 (21.9%) cases, while fan-shaped shadowing was rare (4/192 (2.1%)). Tumor borders were found to be irregular in 103/195 (52.8%) cases. Moderate or rich vascularization was observed in 127/187 (67.9%) tumors with reliable color-Doppler information.

There were some differences in ultrasound features between leiomyosarcomas (Figure 3), endometrial stromal sarcomas (Figure 4) and undifferentiated endometrial sarcomas (Figure 5). Leiomyosarcomas were larger than endometrial stromal sarcomas and undifferentiated endometrial sarcomas (median largest diameter 106 mm *vs* 68 mm *vs* 70 mm). Endometrial stromal sarcomas manifested the highest percentage of visible normal endometrium (44/48 (91.7%)) and regular tumor borders (29/48 (60.4%)), and were less vascularized than the other sarcomas (color score of 1 or 2 in 20/47 (42.6%) tumors with reliable color-Doppler information).

Undifferentiated endometrial sarcomas had the highest rate of absent shadowing (27/31 (87.1%)), irregular tumor borders (23/31 (74.2%)) and hemorrhagic or ground-glass echogenicity of cyst fluid (6/15 (40.0%)). Endometrial stromal sarcoma was the type of sarcoma most often misclassified as benign (13/48 (27.1%)), while undifferentiated sarcoma was the type least often misclassified as benign (1/31 (3.2%)). Ultrasound features of uterine sarcomas that were misclassified as benign *vs* those correctly classified as malignant by the original ultrasound examiner are shown in Table S1. Tumors judged to be benign more often had visible normal myometrium (36/40 (90.0%) *vs* 111/153 (72.5%)), visible endometrium (28/40 (70.0%) *vs* 65/153 (42.5%)), homogeneous echogenicity of the solid tissue (22/40 (55.0%) *vs* 21/153 (13.7%)), absence of cystic areas (32/40 (80.0%) *vs* 74/153 (48.4%)), regular tumor border (30/40 (75.0%) *vs* 61/153 (39.9%)) and color score of 1 or 2 (22/40 (55.0%) *vs* 38/153 (24.8%)) than those judged to be malignant.

Most sarcomas (> 80%) were described as not being typical of a benign myoma both by the original ultrasound examiners and by the examiners in the consensus meeting. Other results differed slightly between the examiners. In the consensus meeting, visible normal myometrium was reported less often (53.5% *vs* 76.4%), while inhomogeneous echogenicity of the solid tissue of the lesion, cystic areas, irregular tumor border and fan-shaped shadowing were reported more often (91.2% *vs* 77.8%; 54.7% *vs* 44.6%; 62.1% *vs* 52.8%; and 11.7% *vs* 2.1%, respectively). At the consensus meeting, the prevalence of a 'cooked appearance' of the solid tissue was 21.7%.

DISCUSSION

We have described the clinical and ultrasound characteristics of uterine sarcomas. Only 10% of patients with a sarcoma were asymptomatic, the most common presenting symptom being abnormal vaginal bleeding. On ultrasound, sarcomas typically appeared as isolated large solid masses with inhomogeneous echogenicity of the solid tissue, sometimes containing cystic (usually irregular) areas and usually not manifesting shadowing or calcifications. Although most sarcomas were moderately or well vascularized, a third demonstrated minimal or absent vascularization. Fourteen percent of the sarcomas were described as having ultrasound signs typical of a benign myoma, and 20% were classified as benign by the original ultrasound examiner. Endometrial stromal sarcoma was the type of sarcoma most often misclassified as benign on ultrasound, while undifferentiated sarcoma was the one least often misclassified as benign.

Our study provides information on an area that is poorly covered in the literature. To our knowledge, this is the largest study describing ultrasound findings in uterine sarcomas. The analysis performed during the consensus meeting is another strength of this study. In the consensus meeting, predefined variables and definitions of variable categories were first agreed upon and then used by 16 ultrasound examiners to describe the ultrasound images of the sarcomas, which makes it probable that our results are generalizable. A limitation of our study is that it was retrospective, meaning that some information could not be retrieved and, when reviewing saved images, the ultrasound examiners knew the diagnosis, which may have introduced bias.

Our results are in agreement with information in publications describing the clinical characteristics of uterine sarcomas, in that most patients were symptomatic[1,34], and leiomyosarcomas were diagnosed mainly in postmenopausal women, while more than 50% of patients with endometrial stromal sarcomas were premenopausal[34].

Several studies have described the sonographic appearance of uterine sarcomas (Table S2)[48–62], all of which were small and used few ultrasound variables to describe the ultrasound images, and leiomyosarcomas, endometrial stromal sarcomas and undifferentiated stromal sarcomas were usually not described separately. Exacoustos *et al.*[48], in the largest published series of leiomyosarcomas ($n = 8$), found that they are usually large (largest diameter > 8 cm in seven of eight cases), manifest inhomogeneous echogenicity of the solid tissue and often (in 50% of cases) contain cystic areas. They found rich central vascularization in seven of the eight leiomyosarcomas[48]. We found that about a quarter of the leiomyosarcomas manifested minimal or absent vascularization, and the prevalence of minimal or absent central vascularization according to the consensus meeting was 35.5%. It is difficult to explain this discrepancy. To our knowledge, the largest published series describing ultrasound features of endometrial stromal sarcoma includes 10 cases; Park *et al.*[57] described endometrial stromal sarcomas as solid masses with a mean size of 6.2 cm and with internal cystic degeneration in many cases.

Internal shadows and fan-shaped shadowing are characteristics of benign myometrial lesions, such as myomas and adenomyosis[63,64], but seem to be rarer in sarcomas. Bonneau *et al.*[62] analyzed ultrasound findings in 85 benign myomas and 23 uterine malignant myometrial tumors of different types. Uterine malignancies more frequently appeared as a single mass with no acoustic shadowing than did benign myomas. In our series, internal shadows could be detected in about 20% of the sarcomas, while fan-shaped shadowing was described in only 2% of cases. Calcifications were found in about 10% of the sarcomas in our series. Bonneau *et al.*[62] described ultrasound signs of calcifications in 4/20 (20.0%) benign leiomyomas and in 1/6 (16.7%) sarcomas, and Pekindil *et al.*[58] described one case of endometrial stromal sarcoma with ultrasound signs of calcifications verified histologically. Results regarding calcifications in uterine leiomyosarcomas visible on magnetic resonance imaging are conflicting[65,66].

Two ultrasound examiners (D.J. and A.C.T.) proposed an ultrasound feature that they called 'cooked appearance' to describe the appearance of solid tissue in uterine sarcomas (Figure 1). They suggest that this echogenicity corresponds to tissue necrosis, which is an important

characteristic of sarcomas on histological examination[15]. Our finding of no or minimal vascularization in about one-third of the sarcomas may also be explained by tumor necrosis. Ultrasound signs of necrosis in pelvic metastases from non-gynecological tumors have been described as heterogeneous, avascular areas of mixed echogenicity with blurred borders radiating to the adjacent vascularized tissue[67]. Some of the participants in the consensus meeting had difficulty understanding the definition of the cooked appearance (the assessment of which is entirely subjective), and so almost 20% of the ratings for the variable were 'impossible to say'. Still, about 20% of the ratings were 'present'.

Misclassifying a sarcoma as a benign myoma may result in delayed treatment or inappropriate surgical treatment, for example morcellation of the sarcoma with tumor spillage and/or tumor-positive resection margins. This is highly likely to worsen the prognosis[68]. About 85% of the uterine sarcomas in our series did not manifest ultrasound signs typical of a benign myoma, and 79% were judged to be clearly malignant or suspicious for malignancy, which is reassuring for the purpose of diagnosis. It is possible that some rare benign types of uterine leiomyoma could be confused with a uterine sarcoma on ultrasound, e.g. cellular leiomyomas or mitotically active leiomyomas. To our knowledge, only Exacoustos *et al.*[48] compared the ultrasound features of cellular uterine leiomyomas with those of uterine sarcomas. They found that 'ordinary' benign leiomyomas and cellular benign leiomyomas manifest similar ultrasound features, while they demonstrated ultrasound characteristics different from those of uterine sarcomas.

In conclusion, this study has shown that the ultrasound finding of a large uterine myometrial tumor with inhomogeneous echogenicity, internal irregular cystic areas, absence of shadows and absence of calcifications in a woman with gynecological symptoms (in particular, abnormal vaginal bleeding) suggests malignancy. The ability of subjective assessment of ultrasound images using the ultrasound features outlined above to discriminate correctly between benign and malignant myometrial tumors can only be evaluated properly in a prospective study. However, because sarcomas are rare tumors, it would be a challenge to conduct such a study, although it should be feasible by involving several large oncological referral centers staffed by highly experienced ultrasound examiners.

Contributing ultrasound centers

University of Bologna, Italy (35 cases);
Catholic University, Rome, Italy (27 cases);
Autonomous University of Barcelona, Spain (25 cases);
University of Pamplona, Spain (18 cases);
Skane University Hospital Malmö, Sweden (18 cases);
European Institute of Oncology, Milan, Italy (17 cases);
University College Hospital of London, UK (14 cases);
National Cancer Institute, Milan, Italy (11 cases);
University of Cagliari, Italy (9 cases);
Tor Vergata, Rome, Italy (7 cases);
Charles University of Prague, Czech Republic (6 cases);
Karolinska Hospital, Stockholm, Sweden (5 cases);
San Gerardo University of Monza, Italy (3 cases).

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Schematic drawings (a) and ultrasound images (b) demonstrating ultrasound features of uterine sarcomas, used during consensus meeting. Low-level cyst fluid is illustrated by showing image of ovarian cyst. Circumferential color score of 3 is illustrated by drawing on top of ultrasound image.

Table S1 Ultrasound characteristics of uterine sarcomas, according to classification as benign or malignant on subjective assessment by original examiner

Table S2 Summary of published studies describing ultrasound features of uterine sarcomas