Color Doppler ultrasonography in the differentiation of uterine sarcomas from uterine leiomyomas

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Summary

Objective: The aim of this study was to investigate uterine vascularity in cases of uterine leiomyomas and uterine sarcomas, as well as to determine the efficiency of uterine blood flow analysis in differentiating between them.

Materials and Methods: Transvaginal color and pulsed Doppler findings obtained from 117 patients with histologically proven uterine leiomyoma and 12 with uterine sarcoma were retrospectively assessed.

Results: The mean intratumoral resistance index (RI) and pulsatility index (PI) were significantly lower and the intratumoral peak systolic velocity (PSV) was significantly higher in patients with sarcomas than in patients with uterine leiomyomas. Marked reduction of RI and PI and increased PSV could be found in 14 of the leiomyoma cases which showed large size and/or necrotic, degenerative and inflammatory changes. When a cut-off value of 0.5 for the RI was considered, the detection rate for uterine sarcoma was 67% and the false-positive rate was 11.8%.

Conclusion: These results suggest that the intratumoral RI detected by color and pulsed Doppler ultrasonography in themselves could be poor for the preoperative differential diagnosis of uterine sarcoma.

Key words: Uterine sarcoma; Uterine leiomyoma; Transvaginal color and pulsed Doppler ultrasonography; Uterine vascularity.

Introduction

Benign and malignant uterine tumors constitute approximately 60% of internal genital tract tumors, the overwhelming majority being leiomyoma with an incidence of over 30% in women over 35 [1]. The incidence of uterine sarcomas is much more infrequent, constituting 1-3% of all gynecological malignancies and 3-7% of uterine malignancies [2]. Their particular significance is due to the fact that they can cause complaints and clinical symptoms similar to leiomyomas while they have a tendency toward aggressive infiltrating growth and early metastasis [3]. Without efficient diagnostic capability there is a real danger that patients who have conservative treatment for leiomyomas, actually suffer from uterine sarcoma [4].

In the past few years ultrasonography has become the most widespread and easily available diagnostic procedure in gynecological practice. The recent advent of a high-frequency transvaginal probe with color and pulsed Doppler facilities provides detailed visualization of the reproductive organs and enables detection of blood flow in the small vascular branches which is undetectable by other non-invasive methods. Transvaginal color Doppler has provided the possibility to assess pelvic vascularity and to study the blood flow characteristics in normal cases and in different uterine pathologies [5-11].

In this study we retrospectively evaluated two-dimensional (2D), color and pulsed Doppler ultrasound findings in both uterine leiomyomas and sarcomas and tried to define the vascular changes in the uterine circulation they cause, as well as to determine the efficiency of uterine blood flow analysis in differentiating between them.

Patients and Methods

Twelve patients with uterine sarcoma (5 endometrial stromal sarcomas (ESS), 4 mixed mesodermal sarcomas (MMS), 3 leiomyosarcomas (LMS) one of which was recidivism) underwent surgery in the 1st Department of Obstetrics and Gynecology of Semmelweis University Medical School, one of the largest centers of gynecological oncology in Hungary, between 1 January 1991 and 31 December 1996. The preoperative 2D, color and pulsed Doppler ultrasound findings were compared with those of the 117 patients with uterine leiomyoma who had had a hysterectomy during the same 6-year period. The median age of these women was 43 years (range 25-72 years) and 13 (11%) were postmenopausal. Details of the patients with uterine sarcoma (e.g. age, menstrual status, symptoms, histological diagnosis, stage of tumor, intratumoral resistance index (RI) and peak systolic velocity (PSV)) are summarized in Table 1. The median age of these women was 49 years (range 25-72 years) and five were premenopausal. Nine patients were referred to our hospital with a suspected diagnosis of uterine sarcoma. In six cases (4 ESS and 2 MMS) histological findings of fractional curettage due to bleeding indicated uterine sarcoma. One patient was operated on because recidivism of leiomyosarcoma was presumed.

All sonograms were performed by the same author (I.Sz.) with an ATL Ultramark 9 (Advanced Technology Laboratories, Seattle, USA) scanner with 5 MHz convex electronic vaginal transducer which is suitable for 2D, color and pulsed Doppler examinations. (Patients who had large tumors also underwent transabdominal scanning with a 3.5 MHz transducer.) The characteristics of this instrument and the execution of the 2D, color and pulsed Doppler examination have been described in great

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detail in a previous paper [11]. Color and pulsed Doppler parameters, including high pass filter, sample volume size and velocity scale were optimized for detection of slow flow. The spatial peak temporal average intensity at the maximum amplitude and minimum gate with a simultaneous color and pulsed Doppler mode was less than 100 mW/cm^2, according to the manufacturer's specifications.

Using the empty-bladder technique longitudinal and transverse scans were performed by B-mode ultrasound. Uterine and pelvic anatomy were first evaluated, then the size of the uterus as well as the endometrial thickness was measured. A search was carried out for uterine masses which altered the normal uterine architecture, and the largest dimensions of the tumor were also measured. Mean diameter was calculated after measuring the three largest dimensions.

Color Doppler was used to depict uterine vascularity and to visualize the main uterine, myometrial and intratumoral vessels. The location and arrangement of the tumor vessels were also analyzed. At the blood flow velocity waveform analysis the pulsed Doppler gate was placed at the region where the color dots were noted, and blood flow velocity waveforms with maximum amplitude and frequency shift were recorded. The resistance index (RI), pulsatility index (PI) and peak systolic velocity (PSV) were determined by spectral analysis of the Doppler frequency shift from the tumor vessels as the average value obtained from five consecutive reproducible waveforms. For PSV measurements, angle correction was not carried out, as it has been shown that this is not required for intratumoral vessels where the gate encompasses a substantial number of vessels [12]. Some signals from certain areas of the same tumor were recorded, but the lowest values of the impedance indices were accepted for final analysis. Color Doppler was also used to identify the main uterine artery at the level of the internal os. The pulsed Doppler gate was placed over the vessel and flow velocity waveforms were recorded. (The transducer was positioned so that the angle between the pulsed Doppler beam and the vessel was close to 0°). After the angle correction a qualitative blood flow analysis of the main uterine arteries was performed.

During the histopathological processing of the surgical specimen low and high grade uterine sarcomas were differentiated on the basis of mitotic numbers per microscopic field [13]. In order to determine the extension of uterine sarcomas, the FIGO method was applied [14].

For computer analysis of the data the program package Statgraphics Version 4.0 (Statistical Graphics Corp.) was used. A difference was considered significant when using the Student's two-sample t-test, p was less than 0.05.

Results

All of the sarcomas displayed deformity (distortion and enlargement) of the uterus and altered echogenicity of the myometrium. The length of the uterus varied from 54 to 142 mm (mean, 100 ± 33.5 mm). The anteroposterior diameters measured 33-95 mm (mean, 66.5 ± 22.4 mm). Disintegration of the normal structure of a significant part or all of the myometrium without defined changes was observed in four cases (1 high and 2 low grade ESS, and 1 MMS) (Figure 1). Predominantly solid masses with irregular borders, which invaded the uterus, were identified in two cases (MMS and ESS of high grade). Fleshy masses producing irregular muscle echoes, similar to leiomyomas, were found in five cases (2 MMS, 2 LMS and 1 low grade ESS). In case 8 (recidivous LMS) a tumor mass (118 x 98 x 112 mm) with irregular borders and mixed (solid and cystic) structure was found.

Details of the patients with uterine sarcoma are shown in Table 1. Intratumoral blood flow was present in all cases of uterine sarcomas. In nine cases irregular, thin, randomly dispersed intratumoral vessels could be detected. Pulsed Doppler signals obtained from these vessels showed low impedance to blood flow. The RI was 0.38 ± 0.07 (range, 0.33 - 0.54), the PI was 0.57 ± 0.31 (range,

Figure 1. — Disintegration of the normal structure of a significant part or all of the myometrium (Histological diagnosis: Endometrial stromal sarcoma /high grade/, FIGO Stage: III).

Table 1. — *Clinical, pathological and blood flow characteristics in 12 uterine sarcoma cases.*

Case	Age at diagnosis	Symptom	Histological diagnosis	FIGO stage	RI (lowest)	PI (lowest)	PSV (cm/s)
1	63	bleeding	mixed mesodermal sarcoma	I	0.35	0.40	12.9
2	65	bleeding	endometrial stromal sarcoma (high grade)	II	0.36	0.42	26.3
3	50	bleeding	leiomyosarcoma	II	0.38	0.40	16.4
4	26*	bleeding	mixed mesodermal sarcoma	I	0.35	0.46	42.2
5	69	bleeding	mixed mesodermal sarcoma	I	0.37	0.40	36.7
6	51	pain	mixed mesodermal sarcoma	IV	0.54	1.16	36.3
7	72	bleeding	leiomyosarcoma	III	0.49	1.10	12.8
8	33*	mass	leiomyosarcoma (recidivism)	III	0.33	0.41	14.1
9	22*	bleeding	endometrial stromal sarcoma (high grade)	III	0.33	0.39	14.3
10	76	bleeding	endometrial stromal sarcoma (low grade)	I	0.76	1.20	13.2
11	35*	bleeding	endometrial stromal sarcoma (low grade)	II	0.65	1.16	23.4
12	25*	bleeding	endometrial stromal sarcoma (low grade)	II	0.55	0.80	21.4

RI, resistance index; PI, pulsatility index; PSV, peak systolic velocity; * premenopausal.

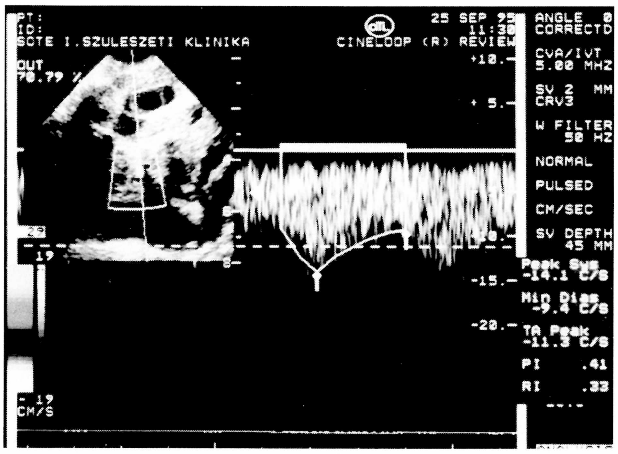

Figure 2. — Pulsed Doppler signal from intratumoral vessels of the tumor mass with mixed (solid and cystic) structure. Low resistance and low PSV. (Histological diagnosis: Leiomyosarcoma (recidivism), FIGO Stage: III).

0.39 - 1.16) while the PSV (cm/s) was 23.55 ± 11.96 (range: 12.8 - 42.2). Irregular vessel arrangement and increased vascularity could not be detected in three cases of the low grade type endometrial stromal sarcoma (ESS). A moderate decrease of vascular impedance (RI 0.65 ± 0.10; range 0.55 - 0.76; PI 1.05 ± 0.22; range 0.80 - 1.20) was recorded in intratumoral vessels. The PSV was 19.33 ± 5.40 (range 13.2-23.4).

A well-circumscribed mass with distinct margins was the typical appearance of the leiomyoma. Uterine length was 71.4 ± 20.1 mm (ranging from 40 to 156 mm) and the mean anteroposterior diameter was 56.6 ± 20.1 mm (ranging from 27 to 146 mm). In 73 cases (62.4%), a solitary fibroid and in 44 cases (37.6%) several nodes were found. The size of the fibroid ranged from 10 to 170 mm, the mean being 51.6 ± 26.3 mm. Subserosal (43.6%) or submucosal (32.4%) locations of the fibroids were usually found. Intramural occurrence was the most infrequent (24%).

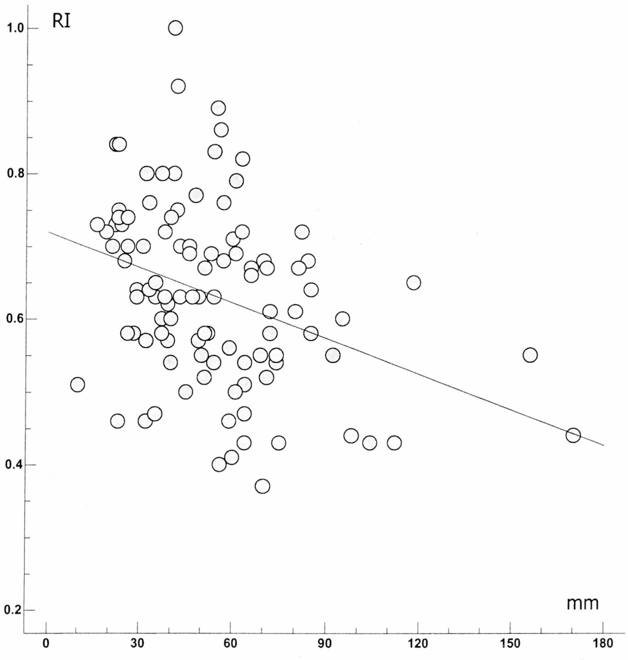

Figure 3. — Negative linear correlation between the intratumoral resistance index (RI) value and size of leiomyomas (r -0.351, p 0.002, linear regression; n: 107).

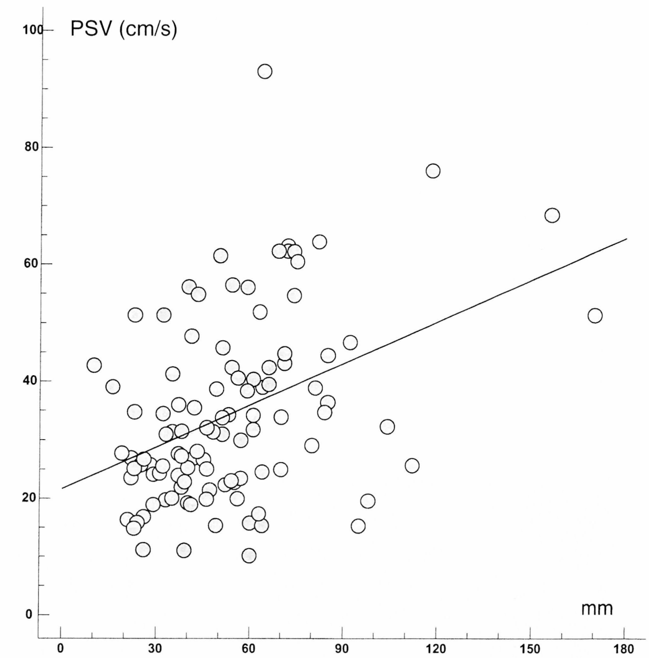

Figure 4. — Positive linear correlation between the intratumoral peak systolic velocity (PSV) value and size of leiomyomas (r 0.402, p 0.001, linear regression; n: 107).

Intratumoral blood flow was detectable in 107 cases (91%) of uterine leiomyomas. Regular, dilated vessels could be identified within the richly or poorly vascularized leiomyomas with peripheral and/or central locations. Pulsed Doppler signals obtained from leiomyoma vessels showed moderate diastolic flow which was always present in fertile ages. The RI was 0.62 ± 0.13 (range 0.37 - 0.92) and the PI was 1.13 ± 0.63 (range 0.4 - 2.9) which were significantly ($p < 0.05$) higher than in the sarcoma group (Table 2). The intratumoral PSV was also higher ($p < 0.05$) in the leiomyoma group than in the sarcoma group. There was no significant difference between the Doppler parameters (RI, PI, PSV, mean velocity) of the main uterine arteries in the uterine leiomyomas and uterine sarcomas.

A correlation was found between the largest dimension of the fibroids and the intratumoral Doppler parameters. The RI and PI decreased and the PSV increased with increased leiomyoma size (Figures 3, 4).

Marked reduction of the vascular impedance (RI 0.44 ± 0.03; range 0.37-0.48; PI 0.59 ± 0.08; range 0.4 - 0.7) and raising of PSV (37.19 ± 17.69, range: 15.3-62.2) could be found in 14 cases which showed large size and/or necrotic, degenerative and inflammatory changes (Figure 5). The size of the fibroids in this group ranged from 23 to 170 mm, the mean being 61.5 ± 21.2 mm.

Table 2. — *Summary of the Doppler parameters of patients in the study.*

	Uterine leiomyomas			Uterine sarcomas	
	n:117			n:12	
	mean ± SD	range	p	mean ± SD	range
Myometrial vessels	n: 107 (91%)			n:12	
RI	0.62 ± 0.13	0.37 - 0.92	$p < 0.005$	0.45 ± 0.14	0.33 - 0.76
PI	1.13 ± 0.63	0.4 - 2.9	$p < 0.05$	0.69 ± 0.36	0.39 - 1.2
PSV (cm/s)	35.7 ± 15.8	10.1 - 93	$p < 0.05$	22.5 ± 10.6	12.8 - 42.2
Main uterine artery	n:117			n:11	
RI	0.77 ± 0.08	0.54 - 1.0	NS	0.76 ± 0.06	0.68 - 0.88
PI	1.74 ± 0.56	0.78 - 3.1	NS	1.68 ± 0.35	1.1 - 2.2
PSV (cm/s)	57.9 ± 19.5	18.5 - 132	NS	58.7 ± 16.9	33.6 - 86.8
MV (cm/s)	27.7 ± 12.1	11.4 - 76.3	NS	32.4 ± 11.9	14.5 - 49.8

RI, resistance index; PI, pulsatility index; PSV, peak systolic velocity; MV, mean velocity.

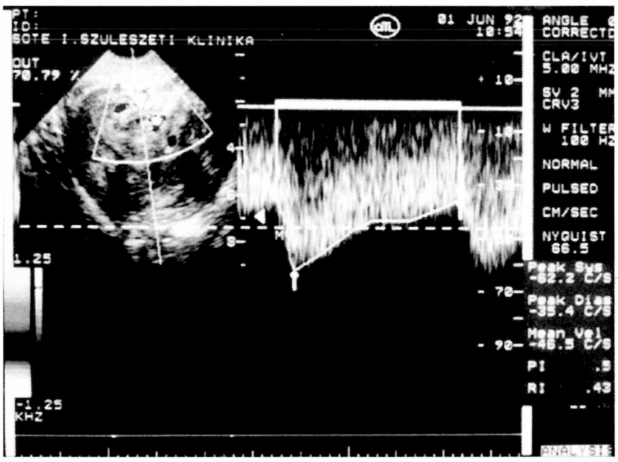

Figure 5. — Pulsed Doppler signal from intratumoral vessel of a large, well-circumscribed mass with distinct margins. Low resistance and high PSV. (Histological diagnosis: Leiomyoma).

When 0.5 (mean RI of uterine leiomyomas plus standard deviation) was considered as the cut-off value of the intratumoral RI alone, eight uterine sarcomas and 14 uterine leiomyomas had RI values below the cut-off value. Table 3 shows a summary of the results on the basis of intratumoral RI < 0.5 alone as a positive finding for detection of uterine sarcoma.

Table 3. — *Cuf-off point 0.5 of intratumoral RI for differentiation between uterine sarcomas and uterine leiomyomas.*

	Histological diagnosis	
	Uterine sarcoma	Uterine leiomyoma
RI < 0.5	8	14
RI > 0.5	4	103

RI, resistance index. Sensitivity 66,6 %; specificity 88.3; positive predictive value, 36.4 %; negative predictive value, 95.8 %; accuracy, 84.8%.

Discussion

The typical sonographic appearance of leiomyoma consists of a mildly to moderately echogenic intrauterine mass that causes nodular distortion of the uterine outline. Echogenicity of the fibroid depends on the relative ratio of fibrous tissue to smooth muscle. With a more fibrous component, there is increased echogenicity of the nodule. A leiomyoma with secondary changes such as degeneration, calcification or necrosis may show mixed echogenicity; that is, it may consist of a mixture of areas with strong echoes and irregular hypoechoic areas [15, 16].

The vascularization of leiomyoma is supported by the pre-existing vessels and normal myometrial vessels originating from terminal branches of the uterine artery. Color Doppler can be used to assess the fibroid vascularity. Kurjak and co-workers detected blood flow in 58-71% of fibroids [9, 17], while Sosic and colleagues found blood flow in 49-100% of leiomyomas [18]. Their results were dependent on the age of the patients (pre- or postmenopause) as well as the size and location of the fibroids. In our study we detected intratumoral blood flow in 91% of the fibroids. Usually solitary vessels with regular placement manifested themselves from the periphery towards the tumor center. Our experiences indicate that intratumoral blood flow is definitely influenced by the size of the fibroid and the intratumoral secondary necrotic, degenerative and inflammatory changes. Kurjak and co-workers particularly mentioned that sometimes uterine leiomyomas with secondary changes exhibit important alterations in their vascular characteristics. A marked reduction in blood flow impedance can be noticed resulting in an overlap with the values for malignant conditions [9].

More than two-thirds of uterine sarcomas develop in postmenopause. They are particularly frequent between 55 and 65 years. The incidence is higher in women who have no children. According to widespread statistics, 50% of sarcomas are MMS. The incidence of LMS is 25-33%, while the rate of ESS is 10-16%. Sarcomas with other histological structures (fibrosarcoma and rhabdomyosarcoma) are very rare. The five-year survival rate depends on tumor stage and age of the patient, the average being around 30%. With respect to survival time, there is no significant difference between tumors of different histological structures [2, 13]. Contrary to published statistics, the incidence of ESS was the highest (5 cases) in our patients with uterine sarcoma. The rate of young patients (6 premenopausal) was relatively high in comparison with the statistical average.

Clinically, a rapid increase in the size of a uterine tumor after menopause arouses suspicion of sarcoma. The signs and symptoms that occur in women with leiomyomas are also produced by sarcomas. Vaginal bleeding, lower abdominal pain, and/or palpable abdominal mass are the usual signs and symptoms [19].

There was no typical sonographic appearance of uterine sarcoma in our cases. Deformity (distortion and enlargement) of the uterus and altered echogenicity of the myometrium was generally detectable with heterogeneous sonographic signs. Cacciatore and colleagues and Kurjak *et al.* detected some sonographic characteristics with similar variety [20, 21]. The diverseness of detected changes can be explained by the differing histological structure and varied extension of sarcomas. The variety of ultrasound characteristics also means that there is no specific sonographic signs of this disease. According to Cacciatore *et al.* and Ezra and co-workers, there are no features which can be detected with 2D ultrasonography on the basis of which uterine sarcomas could be effectively differentiated from leiomyomas [20, 22].

In our group of patients with sarcoma, transvaginal color Doppler sonography showed irregular, thin, randomly dispersed intratumoral vessels, with very low impedance in nine cases (3 cases of LMS, 4 cases of MMS, and 2 high grade ESS), but in three cases of the low grade type ESS, the intratumoral vascularity was indistinguishable from the vascular structure of leiomyomas. The intratumoral blood flow parameters obtained from our patients with uterine sarcoma are well comparable with results of previous studies. Kurjak and colleagues studied ten patients with uterine sarcomas (8 LMS, 1 ESS, 1 sarcoma Botrioides) and compared Doppler values from patients with uterine leiomyomas. The mean intratumoral RI in patients with sarcomas was 0.37 ± 0.03 (ranging from 0.32 to 0.42) which was significantly lower than the mean intratumoral RI (0.54 ± 0.08) in patients with leiomyomas. Using a cut-off point 0.4 of intratumoral RI for discrimination between benign and malignant myometrial tumors, 90.9% sensitivity and 99.8% specificity was found. They had only one false negative case [21]. In one of their previous studies, intratumoral PSV was found to be lower in sarcomas (16.8 ± 6.4 cm/sec) than in leiomyomas (28.4 ± 6.4 cm/sec) [9]. Tepper and co-workers detected abnormal intratumoral vessels with low resistance to blood flow (RI 0.28 ± 0.01) in a high grade ESS, but normal intratumoral vascularity was found in another low grade ESS (RI 0.52 ± 0.01) [23]. Carter *et al.* also did not find increased intratumoral vascularity in a low grade ESS [24]. However, Chen and colleagues identified abnormal intratumoral vascularity with low resistance indices (the lowest RI was 0.38 and 0.41) in two low grade ESS [25]. Hata and co-workers also retrospectively assessed the color and pulsed Doppler findings obtained from 41 patients with histologically proven uterine leiomyoma and five with uterine sarcoma (4 LMS and 1 MMS). They did not find significant differences between the intratumoral RI in uterine leiomyomas and in uterine sarcomas. However, the intratumoral PSV in the uterine sarcomas (71.0 ± 31.7 cm/s) was found to be significantly higher than that in the uterine leiomyomas (22.7 ± 9.2 cm/s). When a cut-off value for the PSV of 41 cm/s was considered, 80% sensitivity and 97.6% specificity was found. The false-positive rate was 2.4% in their study [26].

Conclusions

Varying histological origins, different cellular atypia and mitotic rates of uterine sarcomas can all significantly affect the intratumoral vascularity and blood flow characteristics detected by color Doppler. These variations may also account for results in previous studies which were partly is agreement and partly contradictory. Our results suggest that when using intratumoral RI alone for discrimination an overlap can be found between uterine leiomyomas and uterine sarcomas.

For the present there is no general agreement as to which characteristics obtained from color and pulsed Doppler sonography are the most effective for the differentiation of uterine sarcomas from uterine leiomyomas. It seems that a multiparameter sonographic analysis is required at the examinations of uterine tumors. It is a complex evaluation of all parameters obtained by ultrasonography (morphology and size, vascular arrangement and intratumoral blood flow parameters) which can help extend diagnostic efficiency.

Considering the low number of publications and the conflicting results further prospective studies are required to assess which color Doppler parameters can be used to obtain accurate preoperative differential diagnoses.

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