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[Original article]

The utility of MRI for the preoperative differential diagnosis of uterine sarcoma and leiomyoma: a single-center study

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Abstract

Although uterine sarcoma is a rare disease, its prognosis is extremely poor ; thus, it is important to differentiate it from uterine leiomyoma. In this retrospective study, we examined the association between preoperative MRI findings and postoperative pathology results in 170 patients with uterine tumors who underwent preoperative MRI examination at Fukushima Red Cross Hospital. In 4 cases of sarcoma / smooth muscle tumor of unknown malignant potential (STUMP), abnormal findings were found at a high frequency with T1-weighted imaging (T1WI) (75%), T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and contrast enhancement (CE) (100%). In cases of ordinary leiomyoma, on the other hand, abnormal findings were less frequent. The rates of high DWI signal intensity for degenerated and cellular leiomyoma were 31% and 64%, respectively, and the CE-positive rates were 31% and 57%, respectively. Apparent Diffusion Coefficient (ADC) values appeared to be useful in differentiating degenerated leiomyoma from sarcoma. The relatively characteristic findings of uterine sarcoma on MRI images may overlap with those of degenerated leiomyoma and cellular leiomyoma, making it difficult to diagnose sarcoma on imaging alone. However, findings that distinguish sarcoma from ordinary, degenerated, and cellular leiomyoma cases are worthy of attention, to avoid overlooking sarcoma.

Key words : leiomyoma, uterine sarcoma, degenerated leiomyoma, cellular leiomyoma, MRI findings

Introduction

Uterine leiomyoma is one of the most common diseases of the female reproductive tract, occurring in 20-70% of women of reproductive age[1,2)]. It was reported that at some point in their lives, 30-60% of women experience clinical symptoms such as atypical genital bleeding, pelvic pain, anemia, or infertility, and that about 70% of symptomatic women are being treated with medication and about 30% undergo surgical therapy or interventional radiology[1-3)]. In contrast with leiomyoma, uterine sarcoma is a malignant uterine mesenchymal tumor, and although it is a rare disease with an incidence of about 0.7% per 100,000 women, or 3-7% of all uterine malignancies[4,5)], its prognosis is extremely poor : the 5-year survival rate is 18-68% for leiomyosarcoma (LMS), and the reported recurrence rate is 14-60% for endometrial stromal sarcoma (ESS)[1,5,6)]. Hence, it is important to differentiate between leiomyoma and uterine sarcoma.

The preoperative differential diagnosis of leiomyoma and uterine sarcoma is very difficult when based solely on clinical features. MRI is a highly useful modality for gynecologic tumor detection and characterization, and while conventional MRI makes it relatively easy to differentiate typical leiomyoma from uterine sarcoma, it is often difficult to distinguish sarcoma from atypical leiomyoma cases such as degenerated leiomyoma and cellular leiomyoma[1,6)].

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Advanced MRI techniques such as diffusion-weighted MRI (DWI) may supplement conventional imaging by providing additional physiological and functional information[1,7].

In this retrospective study, we describe the association between preoperative MRI findings and postoperative pathology in patients who underwent surgery, and then, citing relevant literature, discuss MRI findings that are particularly useful for differentiating atypical leiomyoma from uterine sarcoma.

Materials and Methods

One hundred seventy cases of uterine tumors were preoperatively examined by MRI at Fukushima Red Cross Hospital during the 13 months between January 2022 and January 2023 (surgery in 1 case was performed after referral to Fukushima Medical University Hospital). The relationship between preoperative MRI findings and postoperative pathology results was then retrospectively examined in detail.

Analysis of MRI findings

At our department, all patients with uterine tumor are examined with MRI imaging (contrast-enhanced MRI whenever possible) as a preoperative diagnostic tool. Radiologists read all MRI scans ; their comments accompany the scans for preoperative MRI imaging review meetings within our department. In this study, all patients' MRI results and interpretations were used as a reference.

The following aspects of MRI findings were analyzed and evaluated, with reference to the article by Li *et al.* (2016)[8]. [A] T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) : hyperintensity, isointensity, and hypointensity, contrasting with the signal intensity of the outer myometrium. [B] DWI : hyperintensity, isointensity, and hypointensity, contrasting with the signal intensity of the uterine endometrium. [C] Contrast enhancement (CE) : mild, moderate, and obvious signal intensity, contrasting with the signal intensity of the junctional zone and outer myometrium. [D] Apparent diffusion coefficient values (ADCVs) : measurement was performed on an ADC map with a single round region of interest, as large a size as possible, that was placed on the solid homogeneous enhancement areas of tumors with the lowest possible ADC values ; by referring to conventional MRI and carefully avoiding areas of hemorrhage, necrosis, major vascular structures, and artifacts. In each case, the ADCV was measured independently by 3 examiners (HY, RY, and MK), and the average of the 3 values was recorded.

Comparison of the frequency of abnormal MRI findings, laboratory data, etc. between histological types

Three cases of uterine sarcoma, 1 case of smooth muscle tumor of unknown malignant potential (STUMP), 14 cases of cellular leiomyoma, 16 cases of degenerated leiomyoma, and 29 cases of solitary leiomyoma (excluding multiple leiomyomas) among 130 cases of ordinary leiomyoma, were investigated in terms of abnormal findings on contrast-enhanced MRI (T1WI, T2WI, DWI, CE, ADCV), elevated tumor markers (CA125, LDH), and the number and percentage of cases in which patient age was over 55 years.

Statistical analysis was performed using a one-way analysis of variance (ANOVA) and Fisher's exact test. A p value <0.05 was considered statistically significant.

This retrospective clinical study was approved by the Ethics Committee of the Fukushima Red Cross Hospital (approval number : 2022-66), which is guided by local policy, national law, and the World Medical Association Declaration of Helsinki.

Results

Surgical procedure

The surgical procedures in the included patients are shown in Table 1. Of the 128 cases of total hysterectomy, 49 and 79 were performed abdominally and laparoscopically, respectively. Of the 35 cases of myomectomy, 19 and 16 were performed by laparotomy and laparoscopically, respectively. Vagi-

Table 1. Number of cases and results of surgical procedures.

1. No of cases : 170 cases (including 1 surgical case at another hospital)	
2. Surgical procedure :	
#Hysterectomy :	
＊Total abdominal hysterectomy :	49 cases
＊Total laparoscopic hysterectomy :	79 cases
#Myomectomy :	
＊Abdominal myomectomy :	19 cases
＊Laparoscopic myomectomy :	16 cases
#Hysteroscopic surgery :	
＊Transcervical resection :	5 cases

nal myomectomy (hysteroscopic transcervical resection of submucosal myomectomy) was performed in 5 cases.

Histopathology

The postoperative pathology results of the main lesions in each case are shown in Table 2. Among benign tumors, 130 were ordinary leiomyoma, 16 were degenerated leiomyoma, 14 were cellular leiomyoma, 6 were uterine adenomyosis, 2 were adenomatoid tumor, 1 was bizarre leiomyoma, and 1 was neurilemmoma. The breakdown of the 16 cases of degenerated leiomyoma is shown in the table (with duplicates).

Table 2. Postoperative pathological diagnosis (diagnosis of the main lesion#)

＊Ordinary leiomyoma	130 (76.5%)
＊Cellular leiomyoma	14 (8.5%)
＊Adenomyosis	6
＊Adenomatoid tumor	2
＊Bizarre leiomyoma	1
＊Neurolemmoma	1
＊Degenerated leiomyoma	16 (9.4%)
・Hyaline degeneration	9
・Myxoid degeneration	3
・Hydropic degeneration	4
・Fatty degeneration	2
・Ischemic degeneration	1
＊Uterine sarcoma/STUMP	4 (2.4%)
・Leiomyosarcoma	2
・STUMP	1
・Low-grade ESS	1
・High-grade ESS	0

There is some duplication

Three malignant tumors were observed during the study period : 2 cases of leiomyosarcoma, 1 case of low-grade endometrial stromal sarcoma (LGESS), and 1 case of STUMP. MRI images from these 4 cases are shown in Figure 1.

MRI findings in cases of sarcoma, degenerated leiomyoma, and cellular leiomyoma

Figure 1 shows the MRI findings of 4 cases of uterine sarcoma and STUMP. In all 4 cases, T2WI showed high signal intensity, CE was positive (obvious), and DWI showed low signal intensity. T1WI showed high signal intensity in all but 1 case of LGESS. There were some cases of degenerated leiomyoma and cellular leiomyoma with abnormal findings on T2WI, CE, and DWI, as shown in Figures 2 and 3.

Comparison of the frequency of abnormal MRI findings between histological types

Table 3 compares the frequency of abnormal MRI findings and clinical laboratory data between histological types. As also shown in Figure 1, abnormal findings were found at a high frequency in the 4 cases of sarcoma and STUMP, as in previous reports, with abnormal T2WI, DWI, and CE signals

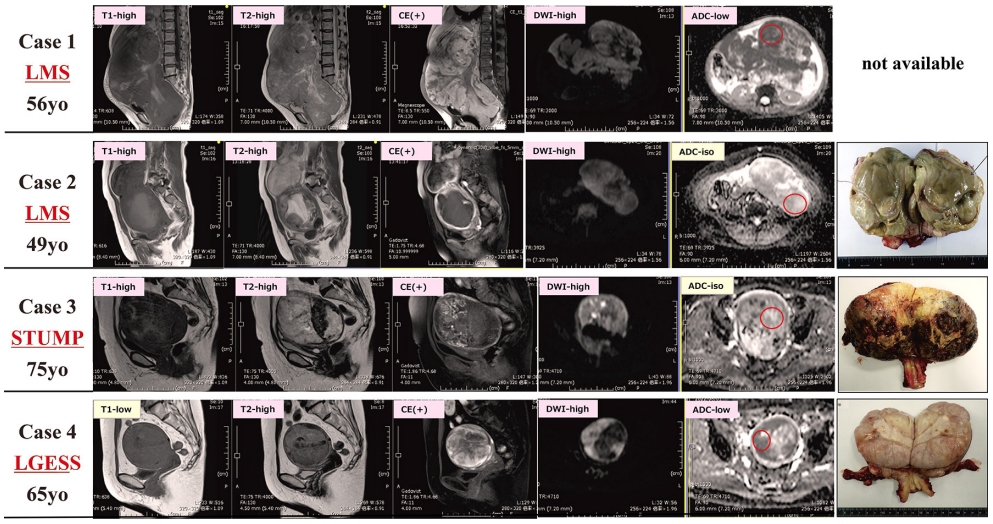

Fig. 1. MRI findings in 4 cases of uterine sarcoma/STUMP
LMS : leiomyosarcoma. STUMP : smooth muscle tumor with uncertain malignant potential. LGESS : low-grade endometrial stromal sarcoma. T1-high : T1-weighted imaging, high signal intensity. T1-low : T1-weighted imaging, low signal intensity. T2-high : T2-weighted imaging, high signal intensity. CE : contrast enhancement, DWI-high : diffusion-weighted imaging, high-signal intensity. ADC : apparent diffusion coefficient.

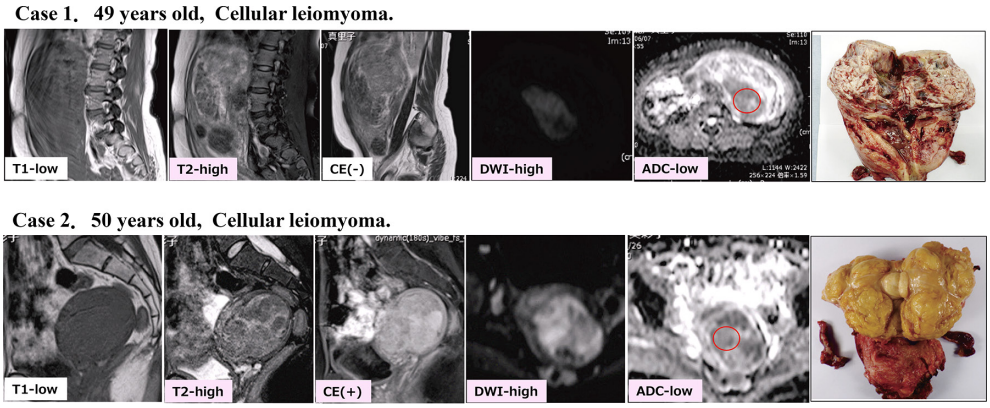

Fig. 2. MRI findings in cellular leiomyoma
T1-low : T1-weighted imaging, low signal intensity. T2-high : T2-weighted imaging, high signal intensity. CE : contrast enhancement, DWI-high : diffusion-weighted imaging, high-signal intensity. ADC : apparent diffusion coefficient.

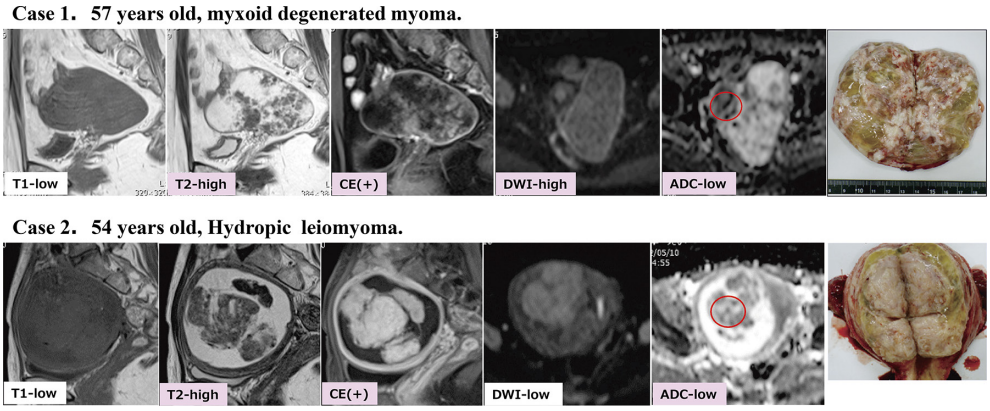

Fig. 3. MRI findings in degenerated leiomyoma.
T1-low : T1-weighted imaging, low signal intensity. T2-high : T2-weighted imaging, high signal intensity. CE : contrast enhancement, DWI-high : diffusion-weighted imaging, high-signal intensity. ADC : apparent diffusion coefficient.

Table 3. Details of MRI findings, tumor markers, and age by postoperative pathology

	Ordinary leiomyoma $N=29$	Degenerated leiomyoma $N=16$	Cellular leiomyoma $N=14$	Sarcoma/STUMP# $N=4$
T1-WI high	0 (0%)	4 (25.0%)	0 (0%)	3 (75%)
T2-WI high	6 (20.7%)	12 (75.0%)	9 (64.3%)	4 (100%)
D-WI high	3 (10.3%)	5 (31.3%)	9 (64.3%)	4 (100%)
ADCV(<1.000)	5 (17.2%)	1 (6.3%)	3 (21.4%)	2 (50%)
ADCV (mm^2/sec)*	1.183±0.180	1.497±0.390	1.116±0.132	1.114±0.232
mean ± SD (range)	(0.851-1.504)	(0.948-2.202)	(0.941-1.370)	(0.863-1.371)
CE**	3 (10.3%)	5 (31.3%)	8 (57.1%)	4 (100%)
CNE***	3 (10.3%)	7 (43.8%)	1 (7.1%)	3 (75%)
CA125 (>35IU/l)	5 (18.5%)	4 (25.0%)	1 (7.1%)	2 (50%)
LDH high	3 (10.3%)	1 (6.30%)	0	2 (50%)
Age ≧ 55 years old	0	2 (16.7%)	1 (11.1%)	3 (75%)

*ADCV : apparent diffusion coefficient value, **CE : contrast enhancement, ***CNE : central non-enhancing area.
red text : ≧ 50%, blue text : 30～49%, black text : 0～29%
#We utilized Fisher's exact test to analyze the incidence of specific MRI characteristics compared to sarcoma/STUMM.
Underlined : there is a significant difference compared to sarcoma/STUMP ($p < 0.05$).

in 4 cases (100%) and abnormal T1WI signals in 3 cases (75%). In ordinary leiomyoma, on the other hand, the incidence of abnormal signals was lower, specifically 0%, 20%, 10%, and 10% in T1WI, T2WI, DWI, and CE, respectively. The rates of high DWI signal intensity (DWI-high) for degenerated and cellular leiomyoma were 31% and 64%, respectively, and those for CE-positive status were 31% and 57%, respectively ; all of these values were higher than those for ordinary leiomyoma. When the frequency of abnormal MRI findings was compared between sarcoma/STUMP and other histological types, significant differences were underlined in the table. A comparison of ADC values among the four histological types was shown in Figure 4. The values were significantly higher in degenerative leiomyoma than in the other histologic types, and there were no significant differences among the other groups.

Discussion

The purpose of this study was to conduct a detailed retrospective review of preoperative MRI findings and postoperative pathology in 170 cases of uterine tumors, with the goal of determining how to avoid missing sarcoma cases when performing a differential diagnosis of uterine sarcoma and leiomyoma (especially, differentiation from cellular leiomyoma and degenerated leiomyoma). MRI is useful in the diagnosis of uterine tumors, especially in the differential diagnosis of leiomyoma and uterine sarcoma. Several recent reports have discussed distinguishing these tumors by using DWI and ADC to compare biofunction[4].

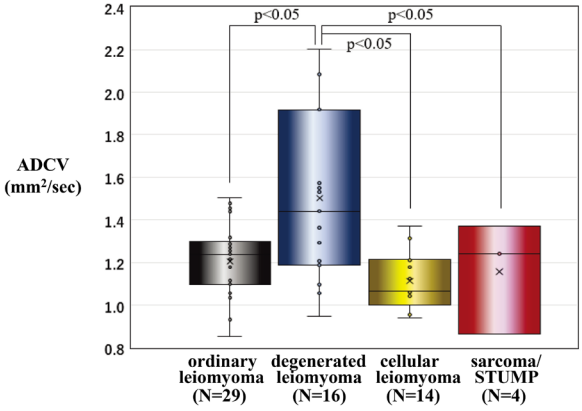

Fig. 4. Comparison of apparent diffusion coefficient values (ADCVs) by pathological diagnosis.
ADCVs were measured independently by 3 examiners (H.Y, R.Y, and M.K.) and their average values were recorded.
We conducted a one-way analysis of variance (ANOVA) to compare the means across different types of uterine tumors. The ADCV in degenerated leiomyoma was significantly higher than the ADCVs in ordinary leiomyoma, cellular leiomyoma, and sarcoma/STUMP ($p<0.05$), and there were no significant differences among the other types of uterine tumor.

Ando *et al.* reported that the presence of a T1WI high-intensity signal area (T1-HIA) within a uterine tumor was important in differentiating leiomyoma from LMS on MRI, and such areas were found in 1.3% of 490 leiomyoma cases compared to 78.6% of 14 LMS cases[6]. Furthermore, there were significant differences between leiomyoma and LMS in terms of the occupying rate of T1-HIA (0.20±0.24 vs 0.42±0.27, respectively, $p<0.05$), homogenous signal uniformity (53% vs 0%, respectively, $p<0.01$), and well-demarcated margins (60% vs 9%, respectively, $p<0.05$)[6]. Another study reported that T1-HIA in LMS reflects coagulative necrotic foci (tumor cell necrosis) within the tumor and is highly suggestive of malignancy, unlike infarct-type necrosis (hyaline necrosis) in leiomyoma, which reflects granulation and vitrification due to hemorrhage[4,9].

Several papers have reported the usefulness of contrast-enhanced MRI (CE-MRI) in differentiating sarcomas (LMS/STUMP) from leiomyoma[10,11]. Lin *et al.* showed that CE-MRI findings, especially central nonenhancement (CNE) findings, were of greater diagnostic value than DWI, T1WI, and T2WI results for the differential diagnosis of 25 rapidly enlarging leiomyomas and 8 LMS/STUMP cases[10]. The authors also reported that the combination of DWI and ADCVs (with the cut-off value of the latter set at 1.08×10^{-3} mm^2/s) provided diagnostic value equivalent to that of CE-MRI, which is useful for patients with suspected sarcoma but who have renal dysfunction that prevents the use of contrast agents.

Distinguishing between degenerated leiomyoma and sarcoma can sometimes be difficult, and DWI and ADCVs can be useful in this regard. Generally, increased cell number and volume, high nuclear-to-cytoplasmic ratio, and limited diffusion of water molecules due to a small extracellular lumen in uterine sarcoma are reflected as decreased ADCVs[8]. Regarding the usefulness of ADCVs, Li *et al.* analyzed 16 LMS and 26 DLM cases and found that the median ADCV was significantly lower in LMS than in degenerated leiomyoma (0.81±0.14 vs 1.22±0.22×10^{-3} mm^2/s, respectively, $p<0.001$)[8]. Furthermore, in an analysis of 33 cases of rapidly enlarging uterine tumors, Lin *et al.* reported that the mean ADCV was significantly lower in 8 LMS/STUMP cases than in 25 degenerated leiomyoma cases (0.89 vs 1.19×10^{-3} mm^2/s, respectively, $p<0.05$)[10].

Wahab *et al.* developed an algorithm to differentiate between 51 cases of uterine sarcoma and 106 cases of benign atypical leiomyoma[12]. First, according to their algorithm, sarcoma is strongly suspected when lymph node enlargement or peritoneal dissemination is present. Second, the combination of T2WI, DWI, and ADCV (cut-off : 0.905×10^{-3} mm^2/s) is used to diagnose a tumor as highly suspect, certainly benign, or probably benign. The sensitivity and specificity of their algorithm for the diagnosis of malignancy were >83% and >94%, respectively, which indicates good accuracy. In short, they reported that in atypical uterine tumors, high T2WI signal intensity (T2WI-high), DWI-high, and an ADCV $\leq0.905\times10^{-3}$ mm^2/s were highly suggestive of sarcoma[12]. There are several reports on the optimal ADCV cut-offs (1.06-1.23 mm^2/s) for the differentiation of uterine sarcomas[8,10,12]. Wahab *et al.* pointed out that a higher ADCV cut-off increases the negative predictive value, but its drawback is that unnecessary total hysterectomy may be performed because a benign leiomyoma is deemed suspicious of malignancy[12].

As mentioned above, MRI findings that are particularly useful in differentiating atypical leiomyoma from sarcoma include T1-HIA, CE on CE-MRI, CNE, and diffusion limited and reduced ADCV on DWI[6,8,10,11]. In this study, the 4 sarcoma/STUMP cases that are shown in Figure 1 also exhibited high rates of T1-HIA (75%), CE (100%), CNE (75%), DWI-high (100%), and low ADCV (50%), but not all findings were necessarily present, even in sarcoma cases (especially in LGESS, which had fewer findings). A well-known and characteristic finding on MRI images of LGESS is a "worm-like" multinodular mass extending into the myometrium, suggesting invasion into the tumor with an intervening normal muscle layer[4]. Although the diagnosis is simple when such typical findings are present, differentiation from leiomyoma or adenomyosis is often problematic because of the difficulty in capturing invasive growths and the fact that LGESS often occurs at a younger age[4].

The results of this study showed that in ordinary leiomyoma, the incidence of abnormal findings was low ; in degenerated leiomyoma, T2WI-high was highly prevalent (75%) while high T1 signal intensity (T1WI-high), DWI-high, CE-positive status, and CNE occurred in 25-44% of cases ; and in cellular myoma, T2WI-high, DWI-high, and CE-positive status were highly prevalent (Table 3). As in previous reports[8,10], the mean ADCV was significantly higher in degenerated leiomyoma than in other histological types (Figure 4), and ADCV was useful for differentiating degenerated leiomyoma from sarcoma, which are difficult to differentiate by other findings. Although the exact mechanisms remain unclear, it is possible that degenerated leiomyomas have abundant water content and are enriched in extracellular matrix with abundant collagen within the legions, and less limited diffusion of water molecules due to a larger extracellular lumen, which may result in increased ADCVs than in other histologic types[8,13,14].

Based on the above MRI findings, the possibility of sarcoma was suspected in 16 (9.5%) of 169 cases operated on at our hospital, and intraoperative rapid pathology was performed ; the details are shown in Table 4. All 3 sarcoma/STUMP cases were preoperatively suspected of being degenerated leiomyoma, but the possibility of sarcoma could not be ruled out. Intraoperative pathology examination was performed in 44% of cases of degenerated leiomyoma and 21% of cases of cellular myomas. Three cases of normal myoma were also diagnosed, all of which occurred in postmenopausal women (61, 62, and 69 years of age) with large tumors.

Other MRI findings that are usually useful in differentiating sarcoma from leiomyoma include tumor diameter, tumor margin (clear or indistinct), and tumor content (homogeneous or heterogeneous).

Table 4. Details of cases in which intraoperative rapid pathology was performed.

Pathology	No. of surgeries	No. of cases of rapid pathology diagnosis	Rate (%)
Ordinary leiomyoma + others	136	3**	2.2%
Degenerated leiomyoma	16	7	43.8%
Cellular leiomyoma	14	3	21.4%
Sarcoma + STUMP	3	3	100%
LMS/LGESS/STUMP	1/1/1	1/1/1	
Total	169*	16	9.5%

*Total surgery cases in Fukushima Red Cross Hospital (169 cases).
**Ordinary leiomyoma cases were all in menopausal with large tumor (61, 62, and 69 years old, respectively).

In addition to imaging results, patient age, menopausal status, and the elevation of tumor markers such as CA125 or LDH have been reported as useful differentiating factors[6,8] ; thus, also considering these may improve the accuracy of sarcoma diagnosis.

Conclusion

The relatively characteristic findings of sarcoma on MRI images (T1WI-high, T2WI-high, CE, DWI-high, etc.) may overlap with degenerated leiomyoma and cellular leiomyoma. ADCV may be useful for differentiating degenerated leiomyoma from sarcoma, which are especially difficult to differentiate by other findings. Although it is difficult to diagnose sarcoma on the basis of imaging alone, all sarcoma/STUMP cases have MRI findings that are different from those of typical ordinary leiomyoma cases, and it seems possible to identify sarcoma cases by keeping in mind the relevant findings. Furthermore, diagnostic accuracy can be further improved by taking into consideration blood test findings, age, and clinical course, in addition to imaging findings. By identifying cases of suspected malignancy without overlooking MRI or other findings, it will be possible to select appropriate surgical procedures, such as laparotomy, as well as to perform tissue retrieval using a surgical collection bag in laparoscopic surgery and prepare for rapid intraoperative pathological examination. It is also important to obtain informed consent preoperatively regarding the possibility of malignancy.

Conflict of interest

The authors have no conflicts of interest to declare.

Patients consent

The authors obtained informed consent from all patients for the publication of this work.

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