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The role of clinical parameters and diffusion magnetic resonance in preoperative evaluation of leiomyomas

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Abstract

Comparing the role of diffusion-weighted imaging magnetic resonance (DWI-MR) in leiomyomas (LM), which can be in pathologically different variants such as cellular, mitotic active, atypical myoma (bizarre nuclei) and STUMP (smooth muscle tumors of uncertain malignant potential), to clinical findings for determining the malignant potential of myoma. Fifty patients who were diagnosed with myoma uteri between March 2013 and April 2017 and evaluated with DWI-MR in the preoperative period were included in the study. Clinical parameters and DWI-MR evaluations of LMs and atypical LMs were compared. While there was no difference in the clinical parameters between LM and atypical LM, there was a significant difference between abnormalities detected by DWI-MR (diffusion restriction, hypervascularity) ($p = 0.012$). DWI-MR may be a guide for preoperative leiomyoma evaluation, especially in patients who are planned to sustain fertility.

Keywords: Atypical leiomyoma, diffusion MR, leiomyoma

Introduction

Leiomyomas (LM) are the most common benign tumors in women in their reproductive period. They are found in approximately 30% of women older than 30 years old and are the most common cause of gynecological surgery [1]. They require treatment when they cause symptoms such as abnormal uterine bleeding, pelvic pain, pelvic compression or infertility.

LMs can be in pathologically different variants such as cellular, mitotic active and atypical myoma (bizarre nuclei) and STUMP (smooth muscle tumors of uncertain malignant potential). The rate of LM variants was found as 1% [2]. In women between the ages of 40 and 50, this rate increases up to 7.5-10% [3].

While leiomyosarcoma (LMS) is very rare, at around 0.4-0.64 / 100,000, undiagnosed LMS is diagnosed in 1: 8300-1: 352 of women operated for LM [4]. The 5-year survival rate of LMS is 30%, and it has a rather poor prognosis [5]. It is clinically not possible to distinguish LMs from LMS. Today, there is not one correct approach to evaluate the malignant potential of LM.

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In the case of hypervascularity detected in ultrasonography, which is the first preferred imaging method, magnetic resonance (MR) imaging should be used. In a study, for evaluation of cellular LMs, its sensitivity was found as 10%, while its specificity was found as 100% [3]. Although standard MR determines the localization of LM in particular, it cannot provide sufficient information in terms of malignant potential [8]. Diffusion-weighted imaging (DWI) is a technique of evaluation based upon the motion of water molecules within a voxel of tissue. This motion can be quantified as an ADC value. The ADC value in solid tissues is considered to be affected by cellular density and the nucleus-cytoplasm ratio. Based on this, the use of DWI-MR can help us demonstrate the malignant potential of myomas [9-11]. However, distinguishing atypical LMs from sarcomatous changes is also rather difficult with DWI-MR [12].

It is difficult to make a decision between LM and LM variants and LMS only by clinical parameters or imaging methods in the preoperative period. Therefore, we aimed to evaluate the role of DWI-MR imaging of LM and atypical LM by comparing clinical parameters in this retrospective study .

Materials and Methods

Patients who were diagnosed with myoma uteri among the patients admitted to the Gynecology Clinic of Baskent University Adana Dr. Turgut Noyan Research Hospital between March 2013 and April 2017 and evaluated with DWI–MR in the preoperative period were included. This study was approved by the Baskent University Institutional Review Board (project no.: KA KA20/129) and supported by the Baskent University Research Fund. Due to the retrospective nature of the study, informed consent was not applicable. Retrospectively, for 624 patients, who were diagnosed LM and operated, files were examined from the data processing system records (Nucleus version 9.3.39; Monad Software and Consulting, Ankara). Patients who were operated preoperatively without evaluations of DWI-MR or doppler transvaginal ultrasonography were excluded from the study. Age, gravid, parity, application complaint, menopausal status and hormone replacement therapy history were evaluated from the demographic data of the patients. Preoperative lactide dehydrogenase enzyme (LDH, U/L) and hemoglobin (hb, gr/dl) levels obtained from the laboratory tests of the patients were examined. Size, number, location (according to FIGO 2011 leiomyoma classification),13 growth pattern and characteristics of myoma in DWI –MR and hypervascularity status in transvaginal doppler ultrasonography were examined. While evaluating the localizations and size of the LM based on DWI-MR, the largest size measured in single and multiple myomas was recorded. The surgical procedure was divided into laparoscopy (LS) and laparotomy (LT), and histopathology results, recurrence, pregnancy status in patients with preserved fertility (myomectomy) were evaluated.

Statistical Analysis

Statistical analysis was performed using the SPSS software (Version 19.0, SPSS Inc., Chicago, IL, USA). If continuous variables were normally distributed, they are presented as mean±standard deviation ($p>0.05$ in Kolmogorov-Smirnov test or Shapira-Wilk $n<30$), and if the continuous variables were not normally distributed, they are presented in median values. The continuous variables were compared using Student t-test or Mann-Whitney U test depending on parametric or non-parametric values, respectively. The categorical variables between the groups were analyzed using Chi-square tests or Fisher's Exact Test. The level for statistical significance was predetermined as $p< 0.05$.

Results

50 patients met the inclusion criteria. 574 patients were excluded from the study because preoperative DWI-MR or transvaginal doppler ultrasonography was not examined.

The mean age of the group who underwent hysterectomy was 44.6 + 4.35, and the mean age of the group who underwent myomectomy was 36.28 + 5.8. The operation indications were abnormal bleeding in 32 patients (64%), pelvic pain in 17 patients (34%) and recurrent in vitro fertilization (IVF) failure in 1 patient. The patient group included in the study had no history of HRT use. The demographic characteristics of the patients are summarized in Table 1.

Table 1. Demographic features of patients

		Mean+ SD
Age (year)		37.9+6
Gravida		0.84+1.3
Menopause status	**premenopausal**	n :48(96%)
	postmenopausal	n:2(4%)
Hb level	**<10g/dl**	n:12(24%)
	>10g/dl	n:38(76%)
LDH		175.8+25.9(U/L)

SD: Standart Deviation of LDH: Lactic Dehydrogenase Enzyme Level
Hb: Hemoglobin g/dl

When the atypical LMs and LMs were compared in terms of their position in the uterus ($p = 0.99$), no significant difference was found. The median number of LM was 2.8 (1-32). The mean size of LMs was 65.9mm + 28.7. The clinical features of LM are summarized in Table 2.

Table 2. Features of myoma

Number of Myoma		2.8(1-32)
TVUSG	**Hypervascularity**	n:10(20%)
Localization of Myoma	**Type1**	n:4(8%)
	Type4	n:24(48%)
	Type5	n:10(20%)
	Type6	n:7(14%)
	Mixed	n:5(10%)
Size of Myoma (mm)	**Mean**	65.9mm+28.7
DWI-MR Features	**No diffusion restriction**	n:30(60%)
	Mild diffusion restriction	n:9(18%)
	Pronounced diffusion restriction	n:5(10%)
	Hypervascularity	n:4(8%)
	Sarcoma suspect	n:2(4%)

TVUSG: Transvaginal Ultrasonography
DWI-MR: Diffusion-Weighted Imaging Magnetic Resonance
* According to Figo 2011 classification

When patients diagnosed with atypical LM and benign LM were classified as “age < 40” and “age > 40”, no significant difference was found between these pathology results ($p = 0.20$). Moreover, according to the pathology results, no significant difference was found while comparing symptoms ($p = 0.09$). When the preoperative hb levels were compared, no significant difference was found in terms of anemia ($p = 0.19$). The serum LDH levels were evaluated in 23 patients, and all were on normal levels. When the ultrasonographic findings of atypical and benign LMs were compared, no significant differences were found ($p = 0.16$).

50% (n: 25) of the patients underwent LS myomectomy, and LMs were removed out of the abdomen by morcellation inside a bag. The procedures that were applied are summarized in Table 3.

Table 3. Type of surgery and Pathology Results

Surgery	**Laparoscopic myomectomy**	n:25(50%)
	Myomectomy with laparotomy	n:14(28%)
	Laparoscopic hysterectomy	n:7(14%)
	Abdominal Hysterectomy	n:3(6%)
	Hysteroscopic myomectomy	n:1(2%)
Pathology	**Benign leiomyom**	n :38(76%)
	Mitotoic active myoma	n:3(6%)
	Cellular Myoma	n:7(14%)
	Myoma with bizarre nuclei	n:1(2%)
	Adenomyosis	n:1(2%)

Diffusion restriction, hypervascularity and sarcomatous change were reported in 20 cases. Atypical LM variations (7 cellular, 3 mitotic active, 1 bizarre nuclei) were reported in 11 patients. Eight of 20 cases reported as abnormal (diffusion restriction, hypervascularity, sarcomatous change) in DWI-MR were diagnosed with atypical LM. When a comparison was made between the cases with abnormal findings in DWI-MR and patients with atypical LM based on their final pathology results, there was a statistically significant difference (p = 0.012). Nine patients had mild diffusion restriction. Cellular LM was detected in 2 of them. 5 patients had pronounced diffusion restriction; two of them were reported as atypical LM. Four patients had hypervascularity. Only one of them was reported as benign LM. In 3 of 30 cases without diffusion restriction, atypical LMs were reported. It was seen that the pathology results of 38 patients were reported as benign LM. The pathology results are summarized in Table 4.

Thirty-three of 50 patients continued their follow-up at our clinic. The mean follow-up period was 25.5 (+ 16.5) months. In the follow-up of 33 operated patients, recurrence LM was detected in 5 patients. When recurrent cases were evaluated based on the pathology results, 1 of them was cellular LM, 1 of them had LM with bizarre nuclei, and the other 3 cases were reported as benign. All of the recurrences happened in the uterus, and no extraperitoneal or distant recurrence was detected. Since no reoperation was required in any patients who had recurrence, their recurrence pathology could not be examined. Among these patients, a new 5 cm LM at the end of 27 months in the 1stpatient, a new 2 cm LM in the 19th month in the 2nd, a new 1 cm LM at the end of 21 months in the 3rdcase, a new 1 cm LM at the end of 21 months in the 4th case and lastly a new 0.8 cm LM in the 5th patient at the end of 13 months were detected. On follow-up, in the patients who were examined by ultrasonography and DWI-MR, there was no application of a patient having recurrence.

Pregnancy was reported in 5 of 40 patients who underwent fertility-preventing surgery. One patient had missed, and 1 of the other 4 patients delivered by caesarean section at the obstetrics department of our clinic. The pathology results were reported in all pregnant women as benign LM.

Discussion

LM is the most common cause of gynecological surgery in women. Today, there is no method or algorithm that can make the preoperative benign / malign distinction in LMs clearly. There are reports on an increasing risk of sarcoma in LMs when the patient is over 40 years old, has single LM which is greater than 6 cm, and there is the presence of a history of radiotherapy / hormonotherapy. The risk of dissemination and unpredictable LMS caused by power morcellation during LS myomectomy restricts the use of minimally invasive methods.

In 2017, Lakhman et al. demonstrated for the first time the importance of MR evaluation in distinction of LMS and atypical LMs [14]. There are only a few articles on the use of DWI-MR in atypical LMs in the literature [9-12]. However, there is no study about comparing between LM and atypical LM by DWI-MR imaging. This is the first study in the published literature. In our study, a significant difference was found between abnormalities detected in DWI-MR (diffusion restriction, hypervascularity) and atypical fibroid pathologies.

Using different methods in preoperative evaluation, with imaging methods to predict this condition, may provide a partial guidance in terms of the treatment and follow-up of patients. The atypical LM concept mentioned in pathology reports that are not evaluated as malignancy in LMs causes uncertainties about how the follow-up process will be after an ordinary myomectomy operation. In our study, 50 patients were operated after preoperative evaluation with diffusion MR, and 11 atypical fibroids were detected. In a review by Sleiman et al., it was reported that 2.5% of atypical LMs could be detected. In the same review, peritoneal dissemination was detected by morcellation at the end of 18 months and had a rate of 0.9% [3]. In our patient group, peritoneal dissemination was not observed in all LS myomectomy cases, because the safe compartment technique (morcellation in handmade bag) was used during morcellation. In another study, a 2% recurrence was detected in cellular LM, while in another study in which 51 atypical LM cases were evaluated, 2 recurrent atypical LMs were detected [15-16]. In our study, recurrence was detected in 5 cases, and no significant difference was observed between LM and atypical LM (p = 2). In the literature, recurrence was detected as LMS after 7 months in a patient with mitotic active LM in hysterectomy material [17].

Being a retrospective study and including only operated patients and a limited number of patients were important factors that restricted our study. It was another handicap that MR images were not evaluated by a single radiologist, and the ADC values that provide objective evaluation were not known. ADC values may make it possible to minimize interobserver variability. Infection,

metabolic diseases, vascular diseases could affect DWI-MR imagining. It was not possible to eliminate of them completely, since the study was not randomized. Additionally, due to the small number of patients, subgroup analysis was not performed in diffusion restriction in DWI-MR. The absence of LMS in the patient group included in the study was a possible result due to the low incidence of LMS, but no comparison could be made between atypical LM and LMS.

In atypical leiomyomas, it is important to follow patients for a long time since recurrence reports are present even after a long break of 87 months, after complete resection such as total hysterectomy [17]. Gynecologists, radiologists and pathologists should be aware of the variants of LM and make the necessary assessments to diagnose this before surgery. The patient should be informed about close follow-up, the risk of recurrence even if it is rare, as well as sarcomatous recurrence.

In conclusion, there is no preoperative method to clearly reveal the malignant potential of LMs. DWI-MR may be guide for preoperative LM evaluation, especially in patients who are planned to sustain fertility. Long-term and randomized controlled studies with more patients are needed.

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Conflict of interest

The authors declare that they have no competing interest.

Financial Disclosure

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Ethical approval

This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki. This study was approved by the Baskent University Medical and Health Sciences Research Board (Project no: KA20 / 129).

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