# **MAJOR PAPER**

# Microcystic, Elongated and Fragmented Pattern Invasion Can Adversely Influence Preoperative Staging for Low-grade Endometrial Carcinoma

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**Purpose:** To investigate the influence of microcystic, elongated and fragmented (MELF) pattern invasion on preoperative evaluation of lymph node (LN) metastasis and myometrial invasion in patients with low-grade endometrial carcinoma.

**Methods:** The study included 192 consecutive patients with low-grade endometrial carcinoma who underwent preoperative computed tomography (CT) and magnetic resonance imaging (MRI), followed by surgery. One hundred sixty one of 192 patients underwent LN dissection and were analyzed for LN metastasis. All patients were analyzed for myometrial invasion. Presence of enlarged LN was evaluated by using size criteria on CT. Depth of myometrial invasion was evaluated on MRI using  $T_2$ -weighted imaging, diffusion-weighted imaging and contrast-enhanced  $T_1$ -weighted imaging comprehensively. Sensitivity and specificity for LN metastasis and deep myometrial invasion were evaluated for MELF group and non-MELF group. The difference of sensitivity between two groups was compared using Chi-square and Fisher's exact test.

**Results:** MELF pattern invasion was identified in 43/192 patients (22%). LN metastases were observed in 18/39 patients in MELF group and 6/122 patients in non-MELF group for pelvic LN and 11/29 patients in MELF group and 4/57 patients in non-MELF group for para-aortic LN. Sensitivity for the detection of pelvic LN metastasis in MELF group was significantly lower than in non-MELF group (16.7% vs 66.7%). As for the assessment of the deep myometiral invasion, pathological deep myometrial invasion were found in 31/43 patients in MELF group and 32/149 patients in non-MELF group. Sensitivity in MELF group showed lower values than in non-MELF group (54.8% vs 78.1% for reader 1, 54.8% vs 62.5% for reader 2), although there was no statistically significant difference (P = 0.09 for reader 1 and P = 0.72 for reader 2).

**Conclusion:** In case of low-grade endometrial carcinoma with MELF pattern invasion, preoperative staging by CT and MRI have a risk for underestimation.

Keywords: MELF, endometrial carcinoma, preoperative staging, computed tomography, magnetic resonance imaging

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### Introduction

Endometrial carcinoma is the most common gynecological tumor in economically developed countries. Because of early symptoms such as abnormal uterine bleeding, endometrial carcinoma is often diagnosed at an early stage with favorable prognosis.<sup>1</sup> However, 15–20% of these tumors recur after surgery, leading to poor prognosis.<sup>2</sup> The International Federation of Gynecology and Obstetrics (FIGO) and the TNM classification are the most widely accepted prognostic classifications.<sup>3,4</sup> They are based on assessment of the extent of myometrial invasion and lymph node and distant metastasis. Other tumor characteristics such as histological type and grade, and lymphovascular space involvement have also been reported as important prognostic factors.<sup>5</sup>

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In the early 2000s, a distinctive pattern of myometrial invasion was introduced by Murray et al.6: the unusual epithelial and stromal changes characterized by microcystic, elongated, and fragmented glands with a fibromyxoid stromal reaction, designated by the acronym 'MELF'.<sup>6</sup> Tumors with MELF pattern invasion show a tendency of increased frequency of deep myometrial and lymphovascular invasion and lymph node metastasis, although MELF pattern invasion is usually found in low grade (grade 1 or 2) endometrial carcinoma because of its sparse pattern of invasion.<sup>7-9</sup> In patients with high-grade endometrial carcinoma, lymphadenectomy is recommended for comprehensive staging and for therapeutic effect. Because patients with low grade and superficial myometrial invasion have a low risk of lymph node metastasis.<sup>10,11</sup> current European guidelines do not recommend lymphadenectomy for these patients.<sup>12</sup> Considering the higher risk of lymph node metastasis in patients with MELF pattern invasion, if they were diagnosed with FIGO stage IA at preoperative staging, there would be a risk of inadequate surgery.

Computed tomography (CT) and magnetic resonance imaging (MRI) are widely used to assess lymph nodes and local tumor extent. Because of its excellent soft-tissue contrast, MRI has proven to be the most accurate imaging modality for assessing the depth of myometrial invasion: it has accuracy of 83–92%.<sup>13</sup> However, we hypothesized that those characteristic pathological features of MELF pattern invasion engender underestimation of preoperative staging by these imaging modalities. No report of the relevant literature describes a study evaluating preoperative staging accuracy in patients with MELF pattern invasion on CT and MRI.

This study was conducted to assess MELF pattern invasion effects on preoperative staging in patients with lowgrade endometrial carcinoma.

# **Materials and Methods**

This study was approved by our Institutional Review Board. Informed consent was waived based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour, and Welfare.

### Patients

From our institutional clinical records of July 2007 through August 2017, we selected consecutive patients with grade 1 or 2 endometrial carcinoma who underwent surgery and preoperative staging by CT and MRI. Two hundred sixty-three patients were identified. Of these, 71 patients were excluded because of a lack of a detectable tumor on MRI (n = 61), prior neoadjuvant chemotherapy (n = 9), or poor quality diffusion-weighted imaging (DWI) with severe motion artifact (n = 1). Finally, this study examined data of 192 patients. All patients had undergone total hysterectomy and bilateral salpingo-oophorectomy. Para-aortic lymphadenectomy was

performed in patients at intermediate to high risk of recurrence, i.e. those with suspicious of deep myometrial invasion, cervical stromal invasion and extra-uterine spread on preoperative imagings. Pelvic lymphadenectomy was routinely performed unless patients were in poor performance status or refused. Of the 192 patients, 74 (38%) underwent only pelvic lymphadenectomy, one (0.005%) underwent left pelvic lymph node (LN) sampling, and 86 (45%) underwent pelvic and para-aortic lymphadenectomy. The remaining 31 patients did not undergo lymphadenectomy. The following data were obtained from the medical records and pathological reports: patient age, tumor histology, depth of myometrial invasion, lymphovascular space invasion (LVSI), lymph node status, and presence of the MELF pattern of myometrial invasion and the details of lymph node resection. Tumors were classified using the 2009 FIGO stage.3 Board-certified pathologists at our institution reported all tumors. Presence of MELF pattern invasion was assessed based on previously established criteria: the presence of microcystic glands, elongated glands or either individual cells or small cluster of cells.<sup>6</sup> Patients were classified into two groups according to the presence or absence of MELF pattern invasion (MELF group or non-MELF group).

### CT and MRI technique

The CT scanning was performed using 16 or 64-multidetector CT scanners (Aquilion 64, Aquilion Prime, Aquilion One; Toshiba Medical Systems Corp., Japan). All scanning was performed from the abdomen to pelvis. Image data were acquired using  $16 \times 1.0$  mm or  $64 \times 0.5$  mm beam collimation, 500 ms rotation time 120 kVp and reconstructed into 5 mm axial images for review. Unless contraindicated, nonionic, iodinated contrast medium (Iomeron350; Eisai Co. Ltd., Tokyo, Japan; Iopamiron300; Bayer HealthCare AG, Osaka, Japan; or Omnipaque300; Daiichi Sankyo Co. Ltd., Tokyo, Japan) was administered intravenously (500 mgI/kg of body weight) at a rate of 2.5 mL/s using a power injector. Contrast-enhanced CT images were obtained 90 s after contrast injection.

MRI was performed using a 1.5T unit (Symphony and Avanto; Siemens Health Care, Erlangen, Germany) or a 3T unit (Trio and Skyra; Siemens Health Care, Erlangen, Germany). Before examination, 20 mg of butyl scopolamine (Buscopan®; Nippon Boehringer Ingelheim Co. Ltd., Tokyo, Japan) was administered to reduce bowel motion, unless contraindicated. Each examination involved sagittal T<sub>1</sub>-weighted image (WI) (TR/TE = 400-655/11-30 ms), axial and sagittal  $T_2WI$  (TR/TE = 3730–7760/81–120 ms) and axial and sagittal DWI (TR/TE = 2300-5900/59-79 ms, *b*-value = 0, 500, 1000 s/mm<sup>2</sup> or 0, 500, 800, 1000 s/mm<sup>2</sup>). Slice thicknesses were 4–6 mm with 1–3 mm gaps. Axial and sagittal contrastenhanced (CE)  $T_1WI$  (Fast spin echo; TR/TE = 450-650/9.3-30 ms, gradient echo; TR/TE = 3.2-3.4/1.2-1.3 ms) were obtained after intravenous injection of gadolinium contrast medium (0.2 mL/kg body weight, Magnevist; Bayer Healthcare Pharmaceuticals, Berlin, Germany or ProHance; Bracco-Eisai Co. Ltd., Tokyo, Japan).

#### Assessment of lymph node metastasis

The analysis for LN metastases was performed in patients who underwent lymphadenectomy. Of the 192 patients, 31 patients who did not undergo lymphadenectomy were excluded, and remaining 161 patients were analyzed. One radiologist with 7 years of experience in gynecological radiology measured lymph nodes and evaluated the presence of metastatic lymph nodes on CT. The reader was blinded to histological results. LNs were divided into three groups for region-specific comparison: para-aortic, right and left pelvic regions. The largest LNs of each region were selected and measured. Positive lymph node metastasis was defined as the short axis longer than 8 mm for round LN (short to long axis (S/L) ratio >0.5) or longer than 10 mm for an enlarged LN (S/L ratio <0.5) in all regions.<sup>14</sup> The CT size of metastatic lymph node was defined as the short axis of the largest LN in the pathologically positive region.

#### Assessment of myometrial invasion

Two radiologists, respectively with 6 and 7 years' experience in gynecological radiology, independently assessed the depth of myometrial invasion. Both readers were blinded to the respective histological results. Individual readers evaluated T<sub>2</sub>WI, DWI, and CE-T<sub>1</sub>WI together as in daily clinical practice and made one MRI diagnosis. When there was a discrepancy in findings between  $T_2WI + DWI$  and CE-T<sub>1</sub>WI, a deeper finding was considered as a final MRI diagnosis. In cases without CE-T<sub>1</sub>WI, the MRI diagnosis was made by  $T_2WI + DWI$ . The depth of myometrial invasion was defined as superficial invasion if the tumor invaded the inner half of the myometrium. It was defined as deep invasion if the tumor invaded half or more of the myometrium.<sup>15</sup> Each reader also noted the presence of cofounding factors affecting the interpretation of myometrial invasion. Included cofounding factors were blurred junctional zone, leiomyoma, adenomyosis, thin myometrium, and extension into the uterine cornua, according to earlier reports.<sup>15,16</sup>

#### Statistical analysis

Statistical analyses were analyzed using a commercially available software package (Medcalc ver. 12.3.0; MedCalc Software bvba, Ostend, Belgium). Differences in clinicopathological characteristics between MELF group and non-MELF group were tested with Chi-square tests and Mann–Whitney tests. The CT sizes of metastatic LN in the MELF group and no-MELF group were compared using Mann–Whitney tests. The sensitivity and specificity of lymph node metastasis and myometrial invasion were calculated for the MELF group and non-MELF group using pathological results as the gold standard. Results for LN metastasis were evaluated on a per-patient basis considering LN region. The pelvic and para-aortic LN were analyzed separately. In pelvic LN analysis, it was defined as the correct diagnosis, when the result on CT and pathology matched in the same region. Regarding analysis of the myometrial invasion, results for readers 1 and 2 were evaluated independently. The differences of sensitivity between MELF group and non-MELF group were compared using Chi-square and Fisher's exact test. The difference in incidence of confounding factors between MELF and non-MELF group in cases with deep myometrial invasion were evaluated using Fisher exact test. Inter-reader agreement for evaluation of myometrial invasion on MRI was calculated using the *k*-statistic as follows: 0.00–0.20 represent slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and .080, almost perfect agreement.<sup>17</sup> Significant difference was inferred for *P* of <0.05.

# Results

#### Patient characteristics

Patient and tumor characteristics are presented in Table 1. Of the 192 patients, 43 patients (22%) had MELF pattern invasion and identified as MELF group, whereas the remaining 149 patients (78%) identified as non-MELF group. The medium age was 59 (range 37–78) years for the MELF group and 54 (range 28–85) years for the non-MELF group (P =0.04). The MELF group was more likely to have deep myometrial invasion (P < 0.01), LVSI (P < 0.01), and lymph node metastasis (P < 0.01).

#### Analysis of lymph node metastasis

Lymph node examination was conducted of 39 patients in the MELF group and 122 patients in non-MELF group. In the MELF group, nine patients had pelvic lymphadenectomy only, one had left pelvic LN sampling only and 29 had pelvic and para-aortic lymphadenectomy. In the non-MELF group, 65 had pelvic lymphadenectomy only and 57 had pelvic and para-aortic lymphadenectomy. Among patients with pathologically deep myometrial invasion, para-aortic lymphadenectomy was performed in 23 of 31 patients in MELF group and 24 of 32 patients in non-MELF group and was omitted in remaining patients (eight patients in MELF group and eight patients in non-MELF group). Underestimation of myometrial invasion was the reason in seven of eight patients in MELF group and three of eight patients in non-MELF group. The remaining reasons were poor performance status (n = 1), patient's intention (n = 1), emergency surgery for bleeding (n = 1) and unknown (n = 3). On the other hand, para-aortic lymphadenectomy was performed in six of 12 patients in the MELF group and 33 of 117 patients in non-MELF group among pathologically superficial myometrial invasion. Overestimation of myometiral invasion was the reason in four of six patients in MELF group and seven of 33 patients in non-MELF group. The remaining reasons were synchronized ovarian carcinoma (n = 6), overestimation of preoperative histology (n = 5),

		MELF ( <i>n</i> = 43)	Non-MELF ( <i>n</i> = 149)	P-value
Median age (range)		59 (37–78)	54 (28-85)	0.037
Grade	I	31 (72%)	109 (73%)	0.95
	11	12 (28%)	40 (27%)	
Myometrial invasion	Deep	31 (72%)	32 (21%)	< 0.001
	Superficial	12 (28%)	117 (79%)	
LVSI	Present	31 (72%)	18 (12%)	< 0.001
	Absent	12 (28%)	131 (88%)	
PLN resection		39* (91%)	122 (82%)	
PLN metastasis		18/39 (46%)	6/122 (5%)	< 0.001
PAN resection		29 (67%)	57 (38%)	
PAN metastasis		11/29 (40%)	4/57 (7%)	0.001

Table 1	Patients	and	tumor	characteristics
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\*One of 39 patients underwent left pelvic lymph nodes sampling. MELF, microcystic elongated and fragmented; LVSI, lymphovascular space invasion; PLN, pelvic lymph node; PAN, para-aortic lymph node.

suspicious of pelvic LN metastasis (n = 4), extra-uterine spread (n = 4), suspicious of cervical stromal invasion (n = 3), large tumor volume (n = 1) and unknown (n = 5).

In the MELF group, 18 of 39 patients had pelvic and 11 of 29 patients had para-aortic lymph node metastasis, whereas six of 122 patients had pelvic and four of 57 patients had para-aortic lymph node metastasis in non-MELF group. The median size of the metastatic lymph node at CT was 4.3 mm (range 2.0-32.8) for MELF group and 7.5 mm (range 2.7–11.0) (P = 0.037) (Fig. 1). The diagnostic performance of CT size criteria was assessed on pelvic and on para-aortic LNs. As for pelvic LNs, the sensitivity for detection of lymph node metastasis was 16.7% (95% CI, 3.6-41.4) for the MELF group and 66.7% (95% CI, 22.3–99.1) for the non-MELF group. The specificities were 100% (95% CI, 83.9-100) for the MELF group and 99.1% (95% CI, 95.3–100) for the non-MELF group, respectively. As for para-aortic LNs, the sensitivity for detection of lymph node metastasis was 9.1% (95% CI, 0.2-41.3) for the MELF group and 0% (95% CI, 0.0-60.2) for the non-MELF group. The respective specificities were 100% (95% CI, 81.5-100) and 100% (95% CI, 93.3-100). The difference of sensitivities between MELF group and non-MELF group was significant at pelvic LNs (P = 0.04) (Table 2).

#### Analysis of myometrial invasion

Histopathological examination revealed that 31 of 43 patients in the MELF group and 32 of 149 patients in the non-MELF group had deep myometrial invasion; the remaining patients had superficial invasion. Contrast-enhanced



**Fig. 1** Size of largest lymph node on CT in the region where pathologically metastatic lymph node was found. Median size in the MELF group is 4.3 mm, compared with 7.5 mm in the non-MELF group (P = 0.037).

MRI was used for 186 of 192 patients. The diagnostic performance of the MRI in assessing the depth of myometrial invasion is presented in Table 3. For both readers, sensitivity for the detection of deep myometrial invasion was lower in the MELF group than in the non-MELF group, although there was no statistically significant difference: 54.8% vs 78.1%, P = 0.009 for reader 1, 54.8% vs 62.5%, P = 0.72 for reader 2. Figure 2 shows an example of false negative case in both readers. The numbers of confounding factors found in cases with deep myometrial invasion are summarized in Table 4. For both readers, the incidence of confounding factors was not statistically different between MELF and non-MELF group.

		MELF	Non-MELF	P-value
PLN metastasis	No. of patients (metastasis/total)	18/39	6/122	_
	Sensitivity	16.7 (3/18)	66.7 (4/6)	0.04
	Specificity	100 (21/21)	99.1 (115/116)	_
PAN metastasis	No. of patients (metastasis/total)	11/29	4/57	_
	Sensitivity	9.1 (1/11)	0 (0/4)	1.0
	Specificity	100 (18/18)	100 (53/53)	-

Table 2 Diagnostic value for Lymph node metastasis at CT

MELF, microcystic elongated and fragmented; PLN, pelvic lymph node; PAN, para-aortic lymph node.

Table 3 Diagnostic value for deep myometrial invasion

	MELF	Non-MELF	P-value
Reader 1			
Sensitivity (%)	54.8 (17/31)	78.1 (25/32)	0.09
Specificity (%)	83.3 (10/12)	92.3 (108/117)	_
Reader 2			
Sensitivity (%)	54.8 (17/31)	62.5 (20/32)	0.72
Specificity (%)	91.7 (11/12)	96.6 (113/117)	_

MELF, microcystic elongated and fragmented.

## Discussion

Results showed that the sensitivity for detection of pelvic lymph node metastasis by CT was significantly lower in the MELF group than in the non-MELF group. The size criterion, a short axis greater than 8-10 mm, has been widely accepted. It has sensitivity of 18-66%.14,18-21 Our result for detection of lymph node metastasis in the non-MELF group was similar to those reported, whereas the result obtained for the MELF group was lower. A possible explanation for this finding is that MELF pattern invasion is associated with isolated tumor cells (ITCs) or micro-metastasis in lymph nodes.<sup>22,23</sup> Actually, ITCs are defined as single or small clusters of tumor cells of <0.2 mm. Micro-metastases are defined as <2 mm.<sup>23</sup> These normal-sized lymph nodes that contain a few tumor cells are indistinguishable from non-metastatic lymph nodes at CT and can engender false-negative results. Recently, several reports have described the superiority of FDG/PET-CT for detecting lymph node metastasis, with pooled sensitivity of 72%.24 However, if limited to small lymph nodes of <4 mm, sensitivity was reported as only 16.7%.<sup>25</sup> In our study, half of the metastatic lymph nodes were found to be <4.3 mm in the MELF group. Therefore, we suspected that improvement of diagnostic accuracy, even by FDG-PET/CT, might be limited for the detection of lymph node metastasis in tumors with MELF pattern invasion.

Our results also show that sensitivity for detection of deep myometrial invasion exhibits a lower value in the MELF group than in the non-MELF group. Although not statistically significant, the sensitivity for detection of deep myometrial invasion in MELF group was about 10-20 points lower than in non-MELF group and low *P*-value (P = 0.09) was found in reader 1. Further study with more sample size is needed to define the difference. The incidence of known confounding factors, such as blurred junctional zone, leiomyoma, adenomyosis, thin myometrium, and extension into the uterine cornua, were not different between MELF and non-MELF group in cases with pathologically deep myometrial invasion, and did not explain the difference in sensitivity on MRI. In fact, MELF pattern invasion is observed in the invasive front of myometrium. The tumor foci are small and are often separated and widely scattered from the easily detectable typical invasive front.<sup>6</sup> For MRI, this histological feature might make accurate assessment of the depth of myometrial invasion difficult. Additionally, we suspected that the fibromyxoid stroma surrounding tumor cells of MELF pattern might also affect the imaging assessment. Usually, a tumor is visualized as having slightly higher signal intensity than normal myometrium on T<sub>2</sub>WI and DWI. On the other hand, the abundant fibrous tissue might decrease the signal intensity on T<sub>2</sub>WI depending on the volume of fibrous and myxoid component and might obscure the tumor-myometrial signal contrast, leading to underestimation of the invasion front.<sup>26</sup>

From examination using transvaginal ultrasound, Eriksson et al.<sup>27</sup> described, in contrast to our report, that the MELF pattern did not affect the preoperative assessment of myometrial invasion. One possibility for this difference might be the difference of patient inclusion criteria. Eriksson et al. included high-grade and advanced-stage endometrial carcinoma, which tend to show deeper invasion. Our study was limited to low-grade endometrial carcinoma and might therefore include more cases bordering on 50% myometrial invasion.



**Fig. 2** Endometrial carcinoma with MELF pattern invasion in a 69-year-old woman: (**a**) sagittal  $T_2$ -weighted image (WI), (**b**) sagittal diffusion weighted image (b = 1000), (**c**) sagittal contrast-enhanced  $T_1$ WI image and (**d** and **e**) hematoxylin and eosin staining. The (**a**) sagittal  $T_2$ WI shows a slightly hyperintense tumor within the endometrial cavity attached to the posterior wall. The boundary between the tumor and the endometrium is unclear on  $T_2$ WI. Tumor invasion was suspected to be limited in the superficial myometrium. Histological examination confirmed deep myometrial invasion with MELF pattern invasion. At lower magnification, invasive adenocarcinoma show microcystic or elongated findings with characteristic inflammatory reaction and fibromyxoid stroma (**d**). At higher magnification, tumor cells are paler, flatter, and show a histiocytoid dispersed appearance (**e**).

Table 4 Confounding factors in cases with deep myometrial inva	sior
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	Reader 1		Reader 2			
	MELF ( <i>n</i> = 31)	Non-MELF ( <i>n</i> = 32)	<i>P</i> -value	MELF ( <i>n</i> = 31)	Non-MELF ( <i>n</i> = 32)	P-value
Blurred junctional zone	0	0	_	14	10	0.31
Leiomyoma	0	0	_	0	0	-
Adenomyosis	3	2	0.62	1	0	0.49
Thin myometrium	7	12	0.27	6	9	0.56
Extension into cornua	7	8	1	11	15	0.45

MELF, microcystic elongated and fragmented.

Our result of sensitivity for deep myometrial invasion was lower than those described in earlier reports with sensitivities of 83–91%.<sup>15,28–33</sup> A possible inter-study difference is patient characteristics. Our study included only low-grade tumors. Highgrade tumors are usually more aggressive and are likely to have deeper myometrial invasion than low-grade tumors. Another possible explanation is heterogeneity of MRI scans. Our study period was 11 years. Therefore, the period included several scanning protocols and parameters. In addition, this study did not use the para-axial plane that has been recommended in recent years in order to align the interpretation conditions to older cases. Soneji et al.<sup>34</sup> showed that MRI staging accuracy in a specialist single-center study with homogeneous protocol can not be replicated in a daily practice setting. They also reported about 70% sensitivity with heterogeneous MRI scans from multiple hospitals, which closely approximates our result.

The number of cases in which para-aortic lymphadenectomy was actually performed in patients with deep myometrial invasion was greater than expected from the sensitivity of this study. This was thought to be because para-aortic lymphadenectomy was performed when the possibility of deep myometrial invasion was suspected even slightly, in order to avoid inappropriate omission in clinical practice. It is consistent with our results that omissions due to underestimation of myometrial invasion were more common in MELF group than in non-MELF group. Given the high frequency of LN metastasis in MELF group, preoperative diagnosis of MELF pattern invasion is important in addition to improving diagnostic accuracy of myometrial invasion to determine the indication of lymphadenectomy. Since the MELF pattern invasion is diagnosed presently on the surgical specimen, it is difficult to know the presence of the MELF pattern invasion before surgery. In this study, we were unable to find specific MR findings for MELF pattern invasion. However, although it is still not specific, higher vascularity and adenomyosis-like findings were reported as characteristics of tumors with MELF pattern invasion in ultrasound.<sup>27</sup> Therefore, it is required to examine imaging features of MRI using radio-pathological correlation and to explore the possibility of inferring MELF pattern invasion before surgery.

This study had several limitations. First, our study was retrospective and small subjects, with only four patients had para-aortic LN metastasis. Second, because of retrospective study, node-to-node analysis of lymph nodes was not performed. In addition, the range and number of lymph node dissections might affect the detection of metastatic LNs. However, the surgery in this study was conducted under a unified guideline at one institution, we thought that the influence of different surgical procedures might be small. Third, there was heterogeneity in the MRI scans, because of a retrospective study and relatively long study period. Fourth, because the number of cases and the observation period were insufficient, the effect on MELF pattern invasion prognosis was not examined.

### Conclusion

Our results show lower sensitivity for detection of lymph node metastases and deep myometrial invasion in patients with MELF pattern invasion. In case of low-grade endometrial carcinoma with MELF pattern invasion, preoperative staging by CT and MRI might present risks for underestimation. Investigating the characteristic imaging features of MRI suggesting MELF pattern invasion is required as the next step.

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# **Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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