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MAJOR PAPER

Evaluating Myometrial Invasion in Endometrial Cancer: Comparison of Reduced Field-of-view Diffusion-weighted Imaging and Dynamic Contrast-enhanced MR Imaging

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Purpose: To compare the diagnostic ability of reduced FOV diffusion-weighted (DW) MR imaging with that of 3D dynamic contrast-enhanced (DCE) MR imaging in evaluating the depth of myometrial invasion in patients with endometrial cancer.

Methods: Three tesla MR images including T_2-weighted imaging, reduced FOV DW imaging and 3D DCE MR imaging in sagittal and oblique axial (short axis) planes in 25 women with surgically proven endometrial cancer were retrospectively evaluated. The depth of myometrial invasion (stage S: < 50% vs stage D: ≥ 50%) on MR imaging was correlated with surgical pathology results.

Results: The 25 endometrial cancers included 16 stage S and 9 stage D tumors. The depth of myometrial invasion could be accurately evaluated in 68% of the cases for T_2-weighted imaging, 92% for 3D DCE MR imaging, and 96% for reduced FOV DW imaging. In two patients with coexisting adenomyosis, both T_2-weighted imaging and 3D DCE MR imaging failed to reveal the deep myometrial invasion, and reduced FOV DW imaging clearly demonstrated the tumor margin in the cases. Combination of reduced FOV DW imaging reading together with T_2-weighted imaging improved the assessment of myometrial invasion with a diagnostic accuracy of up to 100%.

Conclusions: Addition of reduced FOV DW imaging may improve the staging accuracy of MR imaging for endometrial cancer in assessing the depth of myometrial invasion. Especially, reduced FOV DW imaging has an advantage in assessing the depth of myometrial invasion for patients with coexisting adenomyosis. Reduced FOV DW imaging can be an alternative to 3D DCE MR imaging in evaluating myometrial invasion of endometrial cancer without the use of contrast medium.

Keywords: *endometrial cancer, magnetic resonance imaging, diffusion-weighted magnetic resonance imaging, dynamic contrast-enhanced-magnetic resonance imaging, reduced field-of-view*

Introduction

Endometrial cancer is the most common gynecologic malignancy and its prognosis depends on various factors such as tumor stage, depth of myometrial invasion, cervical stromal invasion, lymphovascular invasion, histological grade, and lymphatic nodal status.[1–5] Especially, the assessment of depth of myometrial invasion is important in evaluating endometrial cancer on MR imaging, because it closely correlates with the prevalence of nodal metastasis and the patient's prognosis.[2,3,6–8] Combining T_2-weighted imaging with contrast-enhanced T_1-weighted imaging including dynamic contrast-enhanced (DCE) MR imaging can provide appropriate information for the assessment of myometrial invasion, however, various pathologic factors such as myometrial thinning due to large tumor, coexisting adenomyosis or leiomyoma, extension of the tumor into the cornua, and congenital anomalies, may cause incorrect MR diagnosis of myometrial invasion.[9–14] Diffusion-weighted (DW) imaging demonstrates endometrial cancer as a high signal intensity mass, and can be useful to determine the depth of myometrial invasion.[5,15–18] According to a meta-analysis which investigated radiological staging of myometrial invasion assessing the role of DW imaging, diagnostic accuracy in preoperative detection of deep myometrial invasion in endometrial cancer is high, and DW imaging and DCE MR imaging do not differ in sensitivity and specificity.[19] However, detailed

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evaluation of myometrial invasion on conventional DW imaging may occasionally be difficult due to its relatively low spatial resolution and distortion. Reduced phase direction field-of-view (FOV) technique by using spatially selective phase encoding gradient can offer higher quality DW imaging with improved spatial resolution, without associated phase wrap round artifacts, and with less artifacts related to motion and susceptibility which are commonly observed in larger FOV DW imaging.[20–22] The purpose of this study is to compare the diagnostic performance of reduced FOV DW imaging with that of contrast-enhanced T_1-weighted imaging including DCE MR imaging in evaluating the depth of myometrial invasion in patients with endometrial cancer.

Materials and Methods

Study population

The institutional review board in our hospital approved this retrospective study, and waived the requirement for written informed consent of patients. We cross-referenced the database of the Department of Obstetrics and Gynecology to identify all patients with surgically proven endometrial cancer who had undergone MR examinations including reduced FOV DW imaging and contrast-enhanced T_1-weighted imaging including DCE MR imaging between December 2014 and June 2016. A total of 25 women with a mean age of 60 years (range, 34–80 years) were included in the current retrospective study with histopathologically proven endometrioid adenocarcinomas in 23 patients (17 grade 1, 2 grade 2, 4 grade 3) and serous carcinomas in 2 patients.

Imaging protocol

MR images were obtained by using 3T superconducting units (Discovery MR750, GE Healthcare, Waukesha, WI, USA) with 32 channel body-array torso coils. In each examination, T_2-weighted imaging, reduced FOV DW imaging and contrast-enhanced 3D T_1-weighted imaging including DCE MR imaging in sagittal and oblique axial (short axis of the endometrial cavity) planes were acquired. Fast spin-echo T_2-weighted images were obtained in the sagittal plane with the following parameters: TR/TE 5000/95.1–104.8 msec.; matrix, 352 × 256; number of acquired signals, two; FOV, 28 cm; section thickness/section gap, 3 mm/0.5 mm. Fast spin-echo T_2-weighted images with fat saturation were obtained in the oblique axial plane which was perpendicular to the endometrial cavity as short axis plane with the following parameters: TR/TE, 5000/97–104.7 msec.; matrix, 352 × 256; number of acquired signals, two; FOV, 30–32 cm; section thickness/section gap, 2 mm/1 mm. Axial and/or sagittal conventional DW images of the pelvis were acquired with the following parameters: TR/TE, 4000/51–56.2 msec.; matrix, 128 × 128 for axial images and 96 × 160 for sagittal images; number of signals acquired, four; field of view, 40 cm; section thickness/section gap, 4–5 mm/0 mm; b = 0 and 800 sec/mm^2 for axial images and b = 0 and 1500 sec/mm^2 for sagittal images. Reduced FOV DW images (FOV optimized and constrained undistorted single shot: FOCUS; GE Healthcare) of the uterus were acquired with the following parameters: TR/TE, 4000/55.2–56.8 msec.; matrix, 160 × 80; number of signals acquired, ten; field of view, 20–24 cm × 8–12 cm; section thickness/section gap, 4–6 mm/0 mm; b = 50 and 800 sec/mm^2. A total of 16 slices were acquired in 2 minutes 52 seconds. 3D DCE MR imaging of the pelvis was performed after administration of a gadolinium chelate (0.1 mmol per kilogram of body weight at 2 mL/s) by using a 3D gradient recalled echo T_1-weighted liver acquisition volume acceleration sequence (LAVA; GE Healthcare) with the following parameters: TR/TE, 4.6/2.1 msec.; number of acquired signals, 0.7; matrix, 320 × 192; field of view, 30 cm; section thickness, 3 mm, interpolated to 1.5 mm. Images were acquired at multiple phases of contrast medium enhancement in sagittal plane (pre-contrast and post-contrast at 30, 50, 70, 90 and 110 seconds). After DCE MR imaging, post-contrast 3D gradient recalled echo T_1-weighted LAVA were obtained in the oblique axial plane with the following parameters: TR/TE, 4.1–4.2/1.7 msec.; number of acquired signals, 0.7; matrix, 288 × 224; field of view, 32–40 cm; section thickness, 3 mm, interpolated to 1.5 mm.

Image analysis

The staging accuracies of T_2-weighted imaging, reduced FOV DW imaging and contrast-enhanced 3D T_1-weighted imaging including DCE MR imaging in the assessment of myometrial invasion in sagittal and oblique axial planes were evaluated independently by two radiologists with 25 and 16 years of experience in pelvic MR imaging, respectively. The reviewers were blinded to the histopathologic staging of the lesions. Agreement between the two radiologists was reached in consensus after careful individual evaluation. The depth of myometrial invasion was classified as stage S (superficial invasion: cancer is limited in the endometrium or invades less than 50% of the myometrium) and stage D (deep invasion: cancer invades 50% or more of the myometrium). The depth of myometrial invasion was evaluated on T_2-weighted imaging at first, on reduced FOV DW imaging two weeks later, and on contrast-enhanced 3D T_1-weighted imaging including DCE MR imaging four weeks later. The results were compared with the histologically confirmed depth of myometrial invasion to determine the diagnostic accuracy of T_2-weighted imaging, reduced FOV DW imaging and contrast-enhanced 3D T_1-weighted imaging including DCE MR imaging, respectively. Diagnostic accuracy of MR imaging without the use of contrast medium (combination of reduced FOV DW imaging reading together with T_2-weighted imaging) was also evaluated.

Results

The 25 surgically proven endometrial cancers included 16 stage S and 9 stage D tumors (Table 1). 16 stage S tumors included 15 the International Federation of Gynecology and

Obstetrics (FIGO) stage Ia tumors and one stage II tumor, whereas 9 stage D tumors included 7 stage Ib tumors and 2 stage II tumors. All 25 tumors exhibited high signal intensity on reduced FOV DW imaging with clear margins (Fig. 1). The depth of myometrial invasion was not able to estimate on T_2-weighted images in 8 stage D tumors due to poor tumor-to-myometrium contrast (tumor and adjacent myometrium showed similar signal intensity), or due to poor tumor-to-coexisting adenomyosis contrast, and also not able to estimate on contrast-enhanced 3D T_1-weighted imaging in 2 stage D tumors due to poor tumor-to-coexisting adenomyosis contrast (Figs. 2, 3). The myometrial invasion was not able to estimate on reduced FOV DW imaging in one stage S tumor due to distortion caused by susceptibility artifact from adjacent rectal gas (Fig. 4). Concordance rates between two readers were high (kappa = 0.92 for T_2-weighted imaging, kappa = 1.0 for contrast-enhanced 3D T_1-weighted imaging, and kappa = 0.96 for reduced FOV DW imaging). The depth of myometrial invasion could be accurately evaluated in 68% of the cases (17/25) for T_2-weighted imaging, 92% (23/25) for contrast-enhanced 3D T_1-weighted imaging, and 96% (24/25) for reduced FOV DW imaging. Combination of reduced FOV DW imaging reading together with T_2-weighted imaging improved the assessment of myometrial invasion with a diagnostic accuracy of up to 100%.

Table 1. Diagnostic accuracy of myometrial invasion on MRI

Pathologic stage	Imaging stage									Total
	T_2WI			DCE-MRI			reduced FOV DWI			
	S	D	NE	S	D	NE	S	D	NE	
Stage S	16	0	0	16	0	0	15	0	1*	16
Stage D	0	1	8**	0	7	2***	0	9	0	9
Total	16	1	8	16	7	2	15	9	1	25

S, Superficial myometrial invasion or limited in the endometrium; D, Deep myometrial invasion; NE, Not able to evaluated; *, Due to distortion caused by susceptibility artifact from adjacent rectal gas; **, Due to poor tumor-to-myometrium contrast (6 lesions) and due to poor tumor-to-coexisting adenomyosis contrast (2 lesions); ***, Due to poor tumor-to-coexisting adenomyosis contrast. T_2WI, T_2-weighted images; DCE-MRI, dynamic contrast-enhanced-magnetic resonance imaging; DWI, diffusion-weighted magnetic resonance imaging.

Discussion

Endometrial cancer is the most common malignant tumor in the female pelvis and its incidence is steadily rising because of prolonging life span and escalating levels of obesity.[1–5] The prognosis of endometrial cancer depends on various pathological factors, and among them the depth of myometrial invasion strongly correlates with the risk of lymph node metastasis (3% with superficial myometrial invasion and 46% with deep myometrial invasion) and prognosis of the patients with endometrial cancer.[5–8] The current stage I of FIGO staging system is divided into Ia and Ib according to the depth of myometrial invasion with a one-half cut-off (< 50% vs ≥ 50%). To assess the depth of myometrial invasion, contrast-enhanced T_1-weighted imaging including DCE MR imaging is considered superior to T_2-weighted imaging in determining deep myometrial invasion.[11,13,14] Nowadays, MR examination including T_2-weighted and DCE MR imaging on multiple planes is considered as standard protocol for preoperative assessment of myometrial invasion in women with endometrial cancer.[13] However, contrast-enhanced T_1-weighted imaging requires the administration of gadolinium-containing agents, which have contraindications such as severe renal

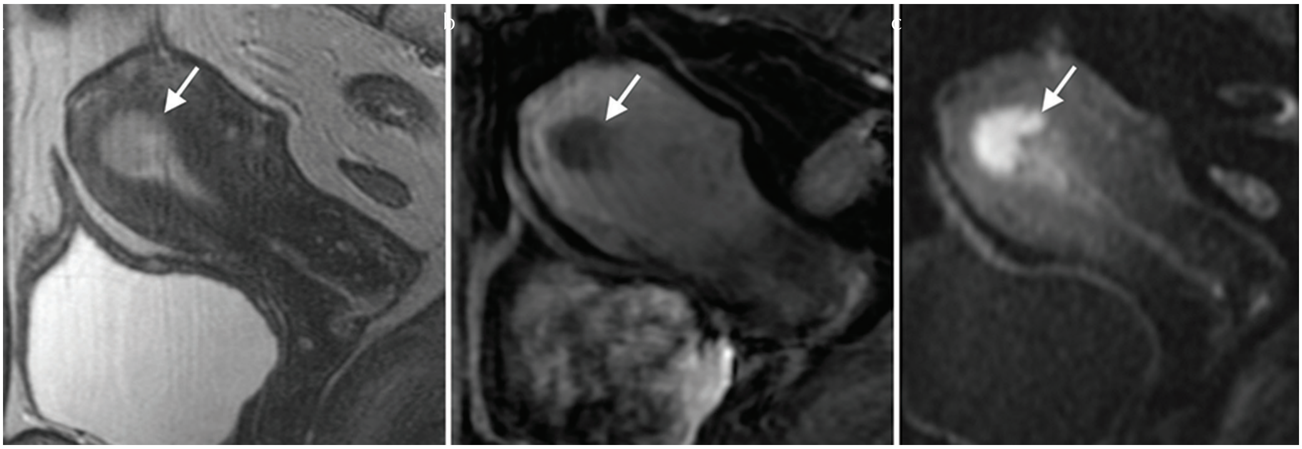

Fig. 1 A 54-year-old woman with endometrial cancer (stage S). (**a**) Sagittal fast spin-echo T_2-weighted image shows intermediate signal intensity endometrial mass (arrow) within the endometrium. No deep myometrial invasion is revealed, however, the boundary between the tumor and the endometrium is not clear due to poor contrast. (**b**) Sagittal contrast-enhanced T_1-weighted imaging shows the tumor (arrow) as low intensity lesion, which contrasts well with well-enhanced myometrium without deep myometrial invasion. (**c**) Sagittal reduced FOV Diffusion-weighted (DW) imaging shows high signal intensity endometrial mass (arrow), which contrasts well with both intermediate signal intensity endometrium and low signal intensity myometrium without deep myometrial invasion.

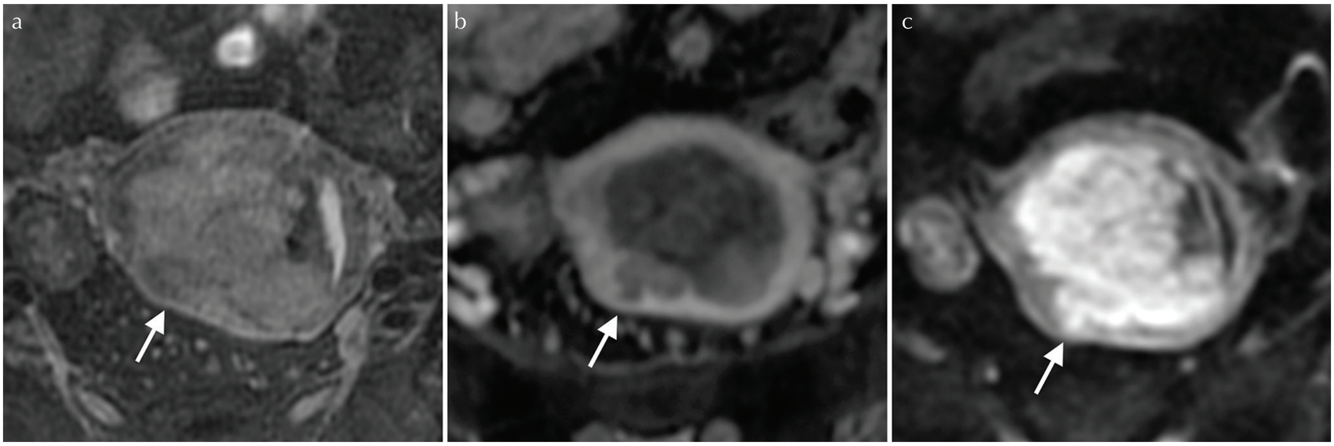

Fig. 2 A 72-year-old woman with endometrial cancer (stage D). (**a**) Oblique axial fast spin-echo T_2-weighted image with fat saturation shows intermediate signal intensity large endometrial mass (arrow). The boundary between the tumor and the myometrium is not clear due to poor contrast, and assessment of the depth of myometrial invasion is not possible. (**b**) Oblique axial contrast-enhanced T_1-weighted imaging shows the tumor (arrow) as low intensity lesion, which contrasts well with well-enhanced myometrium with deep myometrial invasion. (**c**) Oblique axial reduced FOV Diffusion-weighted (DW) imaging shows high signal intensity endometrial mass (arrow), which contrasts well with low signal intensity myometrium with deep myometrial invasion.

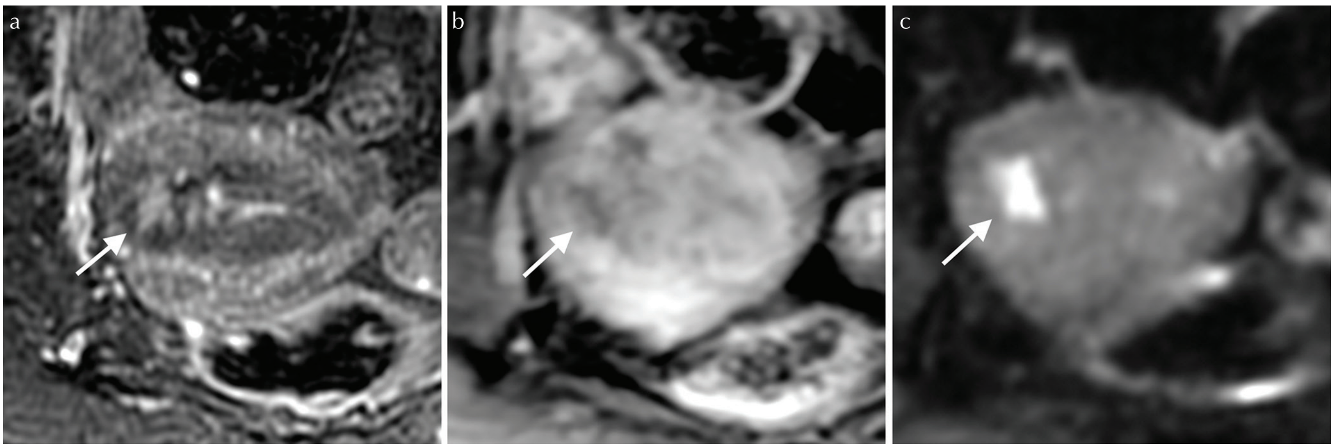

Fig. 3 A 59-year-old woman with endometrial cancer (stage D). (**a**) Oblique axial fast spin-echo T_2-weighted image with fat saturation shows intermediate signal intensity endometrial mass (arrow). The boundary between the tumor and the myometrium is clear, however, the tumor margin adjacent to coexisting adenomyosis is unclear due to poor contrast, and assessment of the depth of myometrial invasion is difficult. (**b**) On oblique axial contrast-enhanced T_1-weighted imaging, the boundary between low intensity tumor (arrow) and heterogeneously enhanced myometrium with coexisting adenomyosis is not clear due to poor contrast, and assessment of the depth of myometrial invasion is not possible. (**c**) Oblique axial reduced FOV Diffusion-weighted (DW) imaging shows high signal intensity endometrial mass with deep myometrial invasion (arrow), which contrasts well with low signal intensity myometrium with coexisting adenomyosis.

dysfunction at risk for nephrogenic systemic fibrosis, allergy to gadolinium-containing agents, or during pregnancy.[5,18] Beddy et al. reported that DW imaging had a higher diagnostic accuracy in assessing the depth of myometrial invasion than did DCE MR imaging.[5] DW imaging has a high diagnostic accuracy in detecting deep myometrial invasion, and there is no significant difference between sensitivity and specificity of DW imaging and DCE MR imaging according to a meta-analysis.[19] Therefore, DW imaging can be an alternative to contrast-enhanced MR imaging in evaluating myometrial invasion of endometrial cancer. However, relatively low spatial resolution for conventional DW imaging, and signal distortion by susceptibility artifacts from intestinal gas may cause misinterpretation of myometrial invasion.

Recently, reduced FOV DW imaging technique called FOV optimized and constrained undistorted single shot (FOCUS) was clinically applied by using a two dimensional spectral spatial excitation radiofrequency pulse, which limits the signal to a small FOV.[20–22] Reduced phase FOV excitation could exclude possible sources of artifacts (i.e. intestinal gas) that are outside the region of interest from the FOV, which may improve local field homogeneity conditions, and minimize

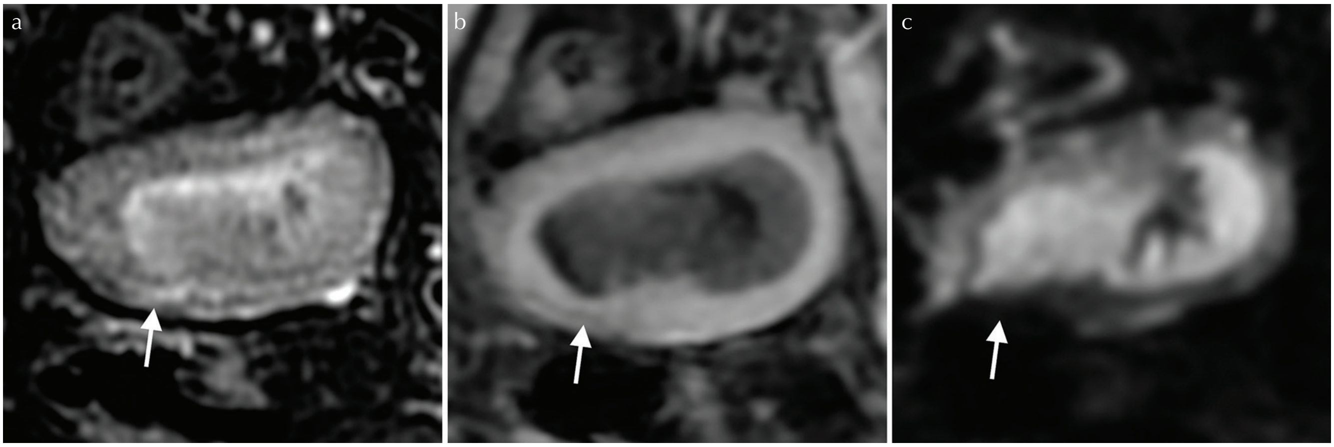

Fig. 4 A 59-year-old woman with endometrial cancer (stage S). (**a**) Oblique axial fast spin-echo T_2-weighted image with fat saturation shows intermediate signal intensity endometrial mass (arrow). The boundary between the tumor and the myometrium is clear with preserved low signal intensity junctional zone. (**b**) Oblique axial contrast-enhanced T_1-weighted imaging shows the tumor (arrow) as low intensity mass, which contrasts well with well-enhanced myometrium without deep myometrial invasion. (**c**) Oblique axial reduced FOV Diffusion-weighted (DW) imaging shows high signal intensity endometrial mass (arrow). Assessment of the depth of myometrial invasion is not possible due to distortion caused by susceptibility artifact from adjacent rectal gas.

off-resonance artifacts due to B0 inhomogeneity, susceptibility gradients, eddy currents, and chemical shift.[20–22] Reduced FOV DW imaging with high spatial resolution may potentially enhance the diagnostic ability in the lesion detection, in the evaluation of tumor extent, and in the differential diagnosis of gynecologic diseases. Especially, severe geometric distortion at air-tissue interfaces around the uterus, ovaries and rectum, which is frequently observed on conventional DW imaging can be minimized on reduced FOV DW imaging. Because conventional DW imaging with larger FOV can cover the whole pelvis for the detection of lymph node metastases, peritoneal dissemination and/or bone metastases, reduced FOV DW imaging is considered not as an alternative for conventional DW imaging but as an additional sequence for the evaluation of local tumor extent.

Bhosale et al. reported the feasibility of reduced FOV DW imaging in the assessment of myometrial invasion in patients with clinical FIGO stage I endometrial cancer. The depth of myometrial invasion was evaluated on sagittal T_2-weighted, reduced FOV DW, and 3D DCE MR imaging by two readers. Compared with T_2-weighted imaging plus DCE MR imaging, reduced FOV DW imaging yielded greater specificity and accuracy for deep myometrial invasion determined by one reader, and greater the sensitivity for deep myometrial invasion determined by another reader.[22] They evaluated the myometrial invasion only on sagittal plane, however, the depth of myometrial invasion should be assessed on multiple planes (i.e. sagittal and oblique axial planes) for the preoperative staging, and this may be a limitation.[13] In our study, the depth of myometrial invasion was assessed on both sagittal and oblique axial planes of T_2-weighted imaging, contrast-enhanced T_1-weighted imaging including DCE MR imaging, and reduced FOV DW imaging.

In the current study, reduced FOV DW imaging was better able to assess the depth of myometrial invasion than T_2-weighted and contrast-enhanced T_1-weighted imaging. On T_2-weighted imaging, the tumor showed intermediate signal intensity similar to that of the outer myometrium in younger patients and that of postmenopausal myometrium, so it was difficult to evaluate the depth of myometrial invasion in eight of nine patients with deep myometrial invasion.[23] In two patients with coexisting adenomyosis, the tumor margins adjacent to adenomyosis were not clear on both T_2-weighted and contrast-enhanced T_1-weighted imaging due to heterogeneous signal intensity and heterogeneous contrast enhancement respectively, and only reduced FOV DW imaging could demonstrate the tumor margins clearly. However typical adenomyosis appears as a low signal intensity area on T_2-weighted images, some adenomyosis may show heterogeneous signal intensity with high intensity areas corresponding to islands of ectopic endometrial tissue and cystic dilatation of glands resulting in the unclear boundaries between the tumor and myometrium.[16,24] Because adenomyosis may show various degrees of contrast enhancement on DCE MR imaging, the heterogeneous enhancement of adenomyosis may cause inaccuracy when evaluating the depth of myometrial invasion of endometrial cancer.[25] Reduced FOV DW imaging clearly demonstrated the boundary between high intensity endometrial cancer and low intensity myometrium in all cases, however, severe distortion caused by susceptibility artifact disabled the assessment of myometrial invasion in one patient, and the depth of myometrial invasion was correctly assessed by reading together with T_2-weighted imaging. Myometrial compression from a bulky polypoid tumor or clots, especially in a senile atrophic uterus, or a tumor extends into the uterine cornua may cause overestimation of myometrial invasion even on reduced FOV DW imaging, and should be considered as potential pitfalls.[26]

Since the retrospective nature, relatively small population (only patients who would undergo surgical resection were included) and range of sequence parameters are limitations to our study, further prospective studies in larger populations to support our results are needed. It was another limitation of our study that comparison of conventional DW imaging and reduced FOV DW imaging was not able to perform because conventional DW imaging was not obtained on multiple planes. Even on reduced FOV DW imaging, signal distortion and ghosting by susceptibility artifacts from intestinal gas may cause misinterpretation of depth of myometrial invasion, so the development of DW imaging with minimized susceptibility artifacts will be required in the future.

Conclusion

Addition of reduced FOV DW imaging may improve the staging accuracy of endometrial cancer in assessing the depth of myometrial invasion. Especially reduced FOV DW imaging has an advantage in assessing the depth of myometrial invasion in cases with coexisting adenomyosis. Reduced FOV DW imaging can be an alternative to contrast-enhanced T_1-weighted imaging including DCE MR imaging in evaluating myometrial invasion of endometrial cancer without the use of contrast medium.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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