

## Diagnostic Accuracy of Preoperative Magnetic Resonance Imaging in Staging Endometrial Cancer: a Five-year Experience

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### ABSTRACT

**Objectives:** To evaluate the accuracy of magnetic resonance imaging (MRI) in predicting deep myometrial invasion, cervical stromal invasion, and pelvic lymph node involvement in the preoperative assessment of women with endometrial cancer.

**Methods:** Patients with endometrial cancer, having preoperative MRI available, and hysterectomy performed in a regional hospital in Hong Kong between 1 January 2010 and 31 December 2014 were included. Those treated with neoadjuvant therapy or without staging MRI were excluded. Primary outcome measure was the correlation between deep myometrial invasion suggested by preoperative MRI and subsequent histopathology of the hysterectomy specimen. Imaging-pathological correlation of cervical stromal invasion and pelvic node involvement was also assessed.

**Results:** Overall 90 women met the criteria and were included in this study. Sensitivity, specificity, and accuracy of preoperative MRI was respectively 83.3%, 88.9%, and 87.8% for predicting deep myometrial invasion; 22.2%, 98.6%, and 83.3% for predicting cervical stromal invasion; and 60.0%, 96.6%, and 91.2% for predicting pelvic node disease.

**Conclusions:** Preoperative MRI is highly accurate in the detection of deep myometrial invasion, which is the single most important prognostic factor. It is moderately accurate and highly specific in the diagnosis of cervical stromal invasion and pelvic node metastasis. The favourable performance of preoperative MRI allows better surgical planning that may then translate into better patient outcome. Although not formally included in the FIGO staging system, it is a highly valuable adjunct in preoperative assessment of women with endometrial cancer.

**Key Words:** Endometrial neoplasms; Lymphatic metastasis; Magnetic resonance imaging; Neoplasm invasiveness; Neoplasm staging

## 中文摘要

### 術前磁共振成像用於子宮內膜癌分期的診斷準確率：五年經驗

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**目的：**評估磁共振成像（MRI）在預測子宮內膜癌患者深肌層浸潤、宮頸間質浸潤和盆腔淋巴結累及的準確性。

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**方法：**研究對象為2010年1月1日至2014年12月31日期間於香港一所分區醫院接受子宮切除術及術前MRI檢查的子宮內膜癌患者。曾接受新輔助療法或無分期MRI的患者不納入本研究。主要評估術前MRI顯示的深部子宮肌層浸潤狀況與子宮切除術標本的組織病理學之間的相關性。此外，對子宮頸間質浸潤和盆腔淋巴結的影像－病理學相關性進行了評估。

**結果：**共90名女性符合標準並納入本研究。術前MRI在預測以下三種病症的靈敏度、特異性和準確度的結果如下：深肌層浸潤為83.3%、88.9%和87.8%；宮頸間質浸潤為22.2%、98.6%和83.3%；盆腔淋巴結疾病為60.0%、96.6%和91.2%。

**結論：**術前MRI檢測深肌層浸潤狀況具有高度準確性，而深肌層浸潤正是一個最重要的預後因素。此外，術前MRI在宮頸間質浸潤和盆腔淋巴結轉移的診斷準確性屬中適度，特異性屬高度。術前MRI的準確性和特異性讓醫生能更好的作手術計劃，繼而轉化為更佳病人預後。雖然術前MRI並未正式納入FIGO分期系統，但可作為一個具相當價值的子宮內膜癌患者術前評估工具。

## INTRODUCTION

Endometrial cancer is the most common gynaecological malignancy in developed countries, including Hong Kong.<sup>1,2</sup> Most tumours are diagnosed early with approximately 80% of them being stage 1 disease at diagnosis.<sup>1,2</sup> The International Federation of Gynecology and Obstetrics (FIGO) staging system is most commonly used to stage endometrial cancer, and systematic lymphadenectomy is recommended as part of the surgical staging.<sup>3</sup> A recent Cochrane systematic review of randomised control trials, however, objected to pelvic and para-aortic lymphadenectomy as a routine procedure during surgery for endometrial carcinoma, due to its uncertain benefits and associated morbidities.<sup>4,6</sup> Management strategies for endometrial cancer depend on tumour staging and grading. For low-risk stage 1 endometrial cancer, hysterectomy with bilateral salpingo-oophorectomy is the standard surgical procedure. For high-to-moderate-risk stage 1 tumour, including those with deep myometrial tumour infiltration, some advocate a tailored approach to systematic lymphadenectomy.<sup>7</sup> Radical hysterectomy followed by pelvic lymphadenectomy is recommended for stage 2 disease. For stage 3 or 4 cancers, treatment is typically individualised and comprises surgical tumour resection including debulking of lymph nodes and other metastatic lesions, followed by chemotherapy and radiotherapy.<sup>1</sup> Surgical planning for endometrial cancer, in particular whether or not to perform lymph node dissection or radical hysterectomy, clearly relies on findings of preoperative magnetic resonance imaging (MRI).<sup>8-12</sup> Nonetheless, the diagnostic accuracy of MRI in staging endometrial cancer varies according to different trials,<sup>13-22</sup> and local data are lacking.

The aim of this study was to evaluate the diagnostic accuracy of MRI in predicting deep myometrial invasion (DMI), cervical stromal invasion (CSI), and pelvic lymph node involvement in the preoperative assessment of a local population of women with endometrial cancer.

## METHODS

Retrospective retrieval of medical notes from operating theatre records and radiology information system was performed. All patients with endometrial cancer who underwent hysterectomy at our institute, which is a tertiary referral centre in Hong Kong, and with preoperative MRI available, were included. Patients treated with neo-adjuvant therapy were excluded, as the final pathology might be down-staged and resulted in bias. Patients with no staging MRI were also excluded. The study period was from 1 January 2010 to 31 December 2014. This study was approved by the institutional review board, with patient consent waived due to its retrospective nature. Each author certified that there was no actual or potential conflict of interests in relation to this paper.

All MRIs were performed with the 1.5T system (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany). The MRI protocol consisted of a combination of T1-weighted (T1W) and T2-weighted (T2W) imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced imaging. Whether or not to image the upper abdomen, or to perform 3D high-resolution T2W imaging was the individual radiologist's decision. Table 1 summarises the standard protocol in our institute for pelvic MRI in the preoperative

**Table 1.** 1.5T magnetic resonance imaging protocol for preoperative evaluation of endometrial cancer.

Protocol	TR (ms)	TE (ms)	Field of view (mm)	Slice thickness (mm)	Voxel size (mm)
T2-HASTE-cor-abdomen (optional)	1000	85	480 x 480	6	1.6 x 1.3 x 6.0
T2-TRUFI-cor-abdomen (optional)	984.33	1.56	480 x 480	4	1.4 x 1.1 x 4.0
T2-TSE-sag	2350	109	250 x 250	5	0.9 x 0.7 x 5.0
T2-TSE-short axis	2370	105	250 x 250	4	0.8 x 0.8 x 4.0
T2-TSE-long axis	3080	105	250 x 250	4	0.8 x 0.8 x 4.0
T1-TSE-tra-whole pelvis	506	7.9	260 x 260	6	1.0 x 0.8 x 6.0
T2-SPC-sag (optional)	1500	132	250 x 250	1	1.0 x 0.8 x 1.0
DWI	6200	85	350 x 306	4	1.8 x 1.8 x 4.0
T1-VIBE-fs-sag	5.45	2.48	350 x 262	2	1.6 x 1.4 x 2.0
T1-VIBE-fs-dyn-C-sag	5.45	2.48	350 x 262	2	1.6 x 1.4 x 2.0
T1-VIBE-fs-delay-C-sag	5.45	2.48	350 x 262.5	2	1.6 x 1.4 x 2.0
T1-VIBE-fs-C-long axis	5.71	2.66	250 x 187.5	2	1.1 x 1.0 x 2.0
T1-VIBE-fs-C-tra-pelvis	5.97	2.75	380 x 214	4	2.1 x 1.5 x 4.0

Abbreviations: DWI = diffusion-weighted imaging; dyn = dynamic; fs = fat-saturated; HASTE = half-Fourier acquisition single-shot turbo spin-echo; TE = echo time; TR = repetition time; TRUFI = true fast imaging with steady-state free precession; TSE = turbo spin echo; VIBE = volumetric interpolated breath-hold examination.

evaluation of endometrial cancer. Short- and long-axis images referred to the axis of the uterus on initial T2W sagittal imaging.

DMI was defined as tumour involvement in >50% of the myometrium in any of the turbo spin echo T2W, 3D T2W, or dynamic contrast enhanced imaging. In our centre, we did not perform DWI in true short or long axis of uterus, thus it was not included in our assessment of DMI. Any invasion of normal T2W hypointensity or smooth enhancement of cervical stroma was defined as CSI. A positive pelvic lymph node was defined as any lymph node with a short axis diameter of >1 cm in any imaging sequence.

All MRI studies were read by radiologist A before the MRI reports and pathology results were revealed. If there was any discrepancy between radiologist A and the reporting radiologists, radiologist B would make the final judgement. Radiologists A and B had two and seven years of experience in gynaecological MRI, respectively.

The primary outcome measure was the correlation between DMI suggested by preoperative MRI and subsequent histopathology of the hysterectomy specimen. Imaging-pathological correlation of CSI and pelvic node involvement were also assessed.

All false-positive and false-negative cases were reviewed by radiologists A and B together in an attempt to identify any pitfalls and possible improvements in image interpretation.

## RESULTS

A total of 92 patients underwent hysterectomy at our institute with preoperative staging MRI available; two patients were excluded due to administration of neoadjuvant chemotherapy. The remaining 90 women fulfilled all the criteria. The mean age of subjects was 55.2 years and endometrial adenocarcinoma was the most frequent diagnosis (96.7%). Most subjects (66.7%) were diagnosed with FIGO stage 1A disease (Table 2). The mean time between staging MRI and surgery was 13.0 (range, 2-137) days. It was exceptionally prolonged in two cases (47 days and 117 days) because surgery was initially refused. All other surgeries were performed within a month of preoperative MRI. In the exceptional two cases, no false-negative result was identified so they were not excluded from the study.

**Table 2.** Staging and histological subtype of the study population.

	No. (%) of patients (n = 90)
FIGO staging	
IA	60 (66.7)
IB	9 (10.0)
II	16 (17.8)
IIIC1	3 (3.3)
IIIC2	2 (2.2)
Histological subtype	
Endometrial adenocarcinoma	87 (96.7)
Serous adenocarcinoma	1 (1.1)
Mucinous adenocarcinoma	1 (1.1)
Clear cell adenocarcinoma	1 (1.1)

Abbreviation: FIGO = International Federation of Gynecology and Obstetrics.

**Table 3.** Sensitivity, specificity, accuracy, PPV, and NPV of preoperative MRI in predicting deep myometrial invasion, cervical stromal invasion, and pelvic lymph node involvement.

	MRI positive	MRI negative	
Deep myometrial invasion			
Pathology positive	TP = 15	FN = 3	PPV = 65.2%
Pathology negative	FP = 8	TN = 64	NPV = 95.5%
	Sensitivity = 83.3%	Specificity = 88.9%	Accuracy = 87.8%
Cervical stromal invasion			
Pathology positive	TP = 4	FN = 14	PPV = 80%
Pathology negative	FP = 1	TN = 71	NPV = 83.5%
	Sensitivity = 22.2%	Specificity = 98.6%	Accuracy = 83.3%
Lymph node metastasis			
Pathology positive	TP = 3	FN = 2	PPV = 75%
Pathology negative	FP = 1	TN = 28	NPV = 93.3%
	Sensitivity = 60.0%	Specificity = 96.6%	Accuracy = 91.2%

Abbreviations: FN = false negative; FP = false positive; MRI = magnetic resonance imaging; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive.

Table 3 summarises the sensitivity, specificity, accuracy, and positive and negative predictive values of preoperative MRI in predicting DMI, CSI, and pelvic lymph node involvement. Diagnostic accuracy of MRI in predicting DMI was high (87.8%); it was also sensitive (83.3%) and specific (88.9%). The accuracy of MRI to predict CSI and positive pelvic node disease was also high (83.3% and 91.2%), mainly due to its high specificity. Their sensitivity was low (22.0% and 60.0%, respectively), however.

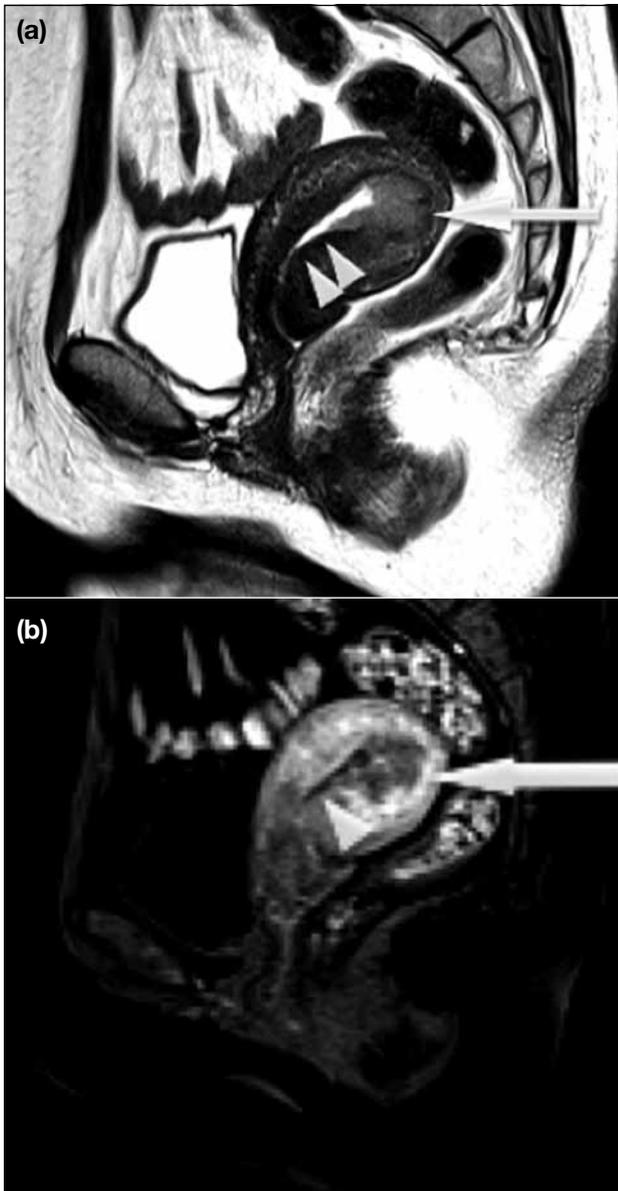
## DISCUSSION

Preoperative MRI is highly accurate in diagnosing DMI, which is the single most important prognostic factor (Figure 1).<sup>23</sup> Our results further substantiate those published in the literature.

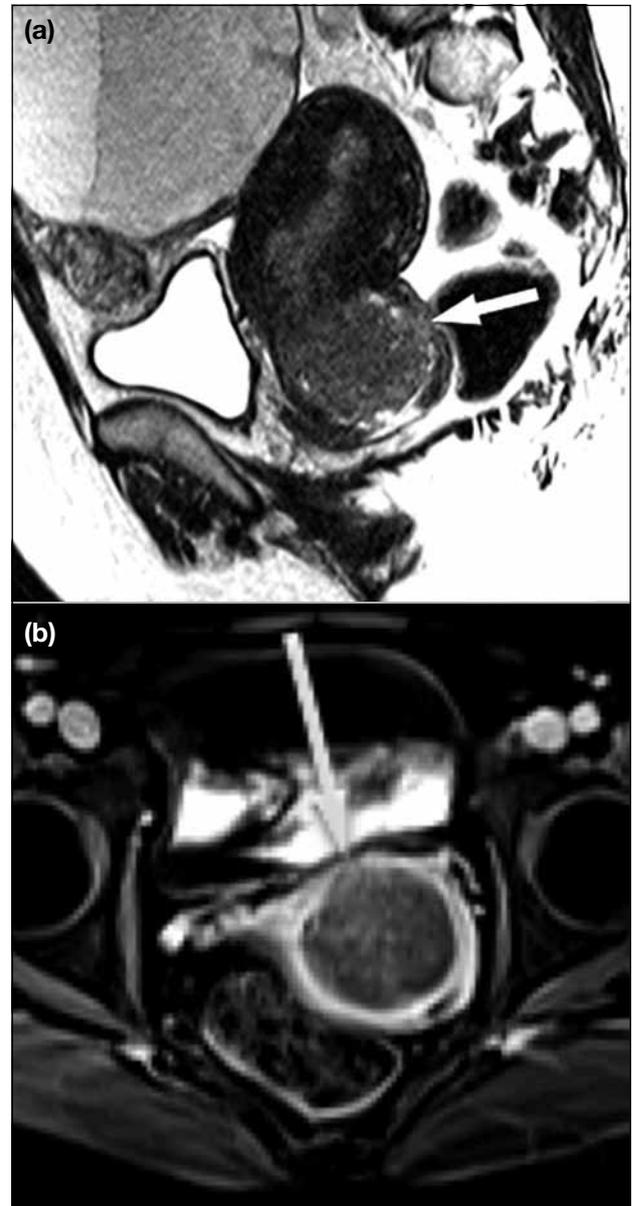
MRI is specific but not sensitive in predicting CSI (Figure 2). A number of factors may explain the false-negative results. First, standard turbo spin echo T2W imaging is of inadequate spatial resolution to detect subtle tumour invasion. In our institute, the spatial resolution of standard turbo spin echo T2W imaging is 5 mm with 10% gap, making detection of tumours with size of <5.5 mm difficult. High-resolution 3D T2W sequence is most valuable to overcome this issue (Figure 3), and is now part of our routine MRI protocol for staging endometrial cancer. Liberal use of orthogonal T2W imaging of the uterine cervix may also be helpful. Second, CSI can present itself only in T2W imaging but not in dynamic contrast study, or vice versa. Abnormalities in either sequence—including irregularity or loss of hypointense ring of cervical

stroma in T2W imaging, and irregularity of cervical mucosal enhancement in dynamic contrast-enhanced T1W imaging—should raise the suspicion of CSI. Lastly, a bulky endometrial tumour with endocervical canal distension makes accurate visualisation of the entire length of the cervix difficult. Subtle tumour infiltration of the upper part of the cervical stroma would be very difficult to identify in this situation (Figure 4).

Likewise, MRI is specific but not very sensitive in the detection of pelvic lymph node metastasis. Lowering the cut-off of MRI positive lymph nodes did not help in this study. Sensitivity remained the same (60.0%) while specificity and accuracy dropped from 96.6% and 91.2% to 89.7% and 85.3%, respectively when the cut-off was lowered from 1 cm to 0.8 cm short-axis diameter. It is therefore reasonable to keep the cut-off at 1 cm. Some authors advocate the use of DWI to differentiate malignant from benign pelvic lymph nodes in gynaecological malignancy.<sup>24,25</sup> This remains controversial, however<sup>26,27</sup> and most positive studies are retrospective in nature with different cut-off values of apparent diffusion coefficient. A prospective case-control trial showed no statistically significant differences in the apparent diffusion coefficient of metastatic and non-metastatic nodes.<sup>26</sup> Both our radiologists and oncologic gynaecologists hesitate to rely solely on DWI at the moment. Thus we do not routinely use DWI to diagnose pelvic nodal disease. We make use of its high detection rate of lymph nodes instead. Our practice may change in the future if more prospective studies show positive results.



**Figure 1.** Deep myometrial tumour invasion (>50%). Sagittal (a) T2-weighted and (b) T1-weighted dynamic contrast-enhanced images showing irregular slightly T2-weighted hyperintense and hypoenhancing endometrial tumour with deep myometrial tumour infiltration (arrows). Only a thin rim of normal outer myometrium is left. Normal hypointense junctional zone is outlined by arrowheads for comparison.

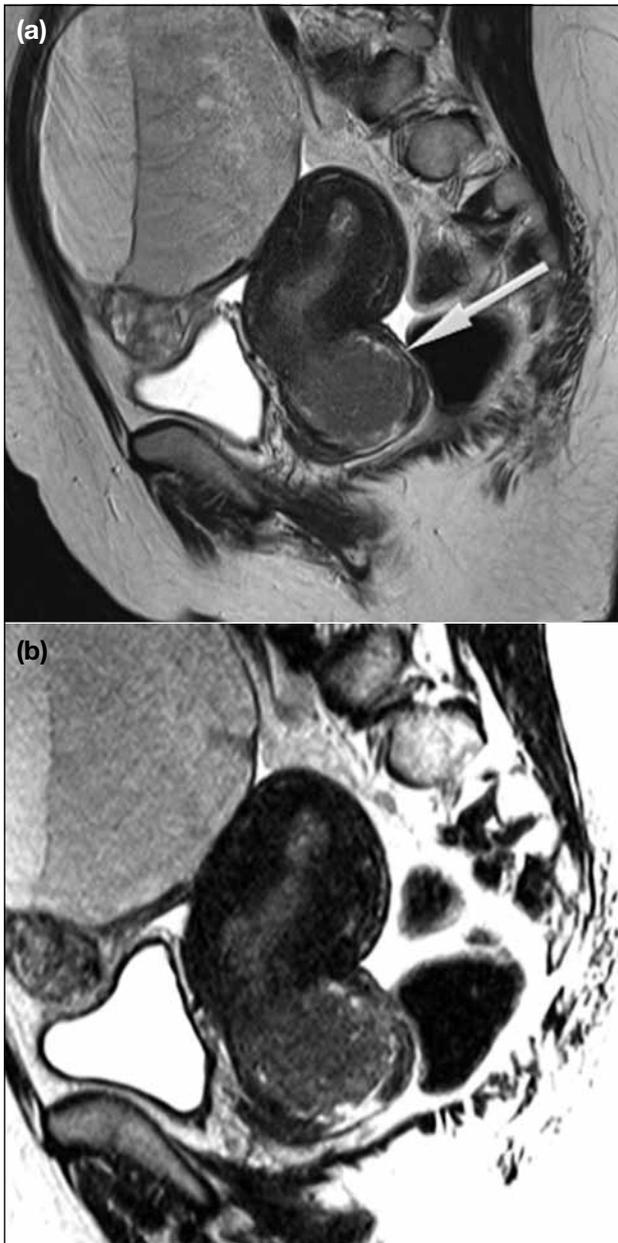


**Figure 2.** Cervical stromal invasion. (a) Sagittal 3D T2-weighted and (b) axial T1-weighted post-gadolinium images showing loss of hypointense, late smooth-enhancing cervical stromal ring at both posterior and anterior walls of uterine cervix (arrows).

Ultra-small superparamagnetic iron oxide nanoparticles are highly sensitive and specific in detection of lymph node metastasis for various tumours, including endometrial cancer.<sup>28-30</sup> A meta-analysis by Will et al<sup>28</sup> concluded the pooled sensitivity and specificity to be 0.88 and 0.96 with similar results found by Rockall et al,<sup>30</sup> with the sensitivity and specificity to detect lymph node metastasis of endometrial cancer approaching

100% and 91%, respectively. Due to safety concerns, however, this lymph node-specific contrast agent was withdrawn from clinical use after a phase III safety and efficacy study.<sup>31</sup> If it is clinically available in the future, the results should be promising.

This study has some limitations. It was a retrospective study so could be prone to more selection and

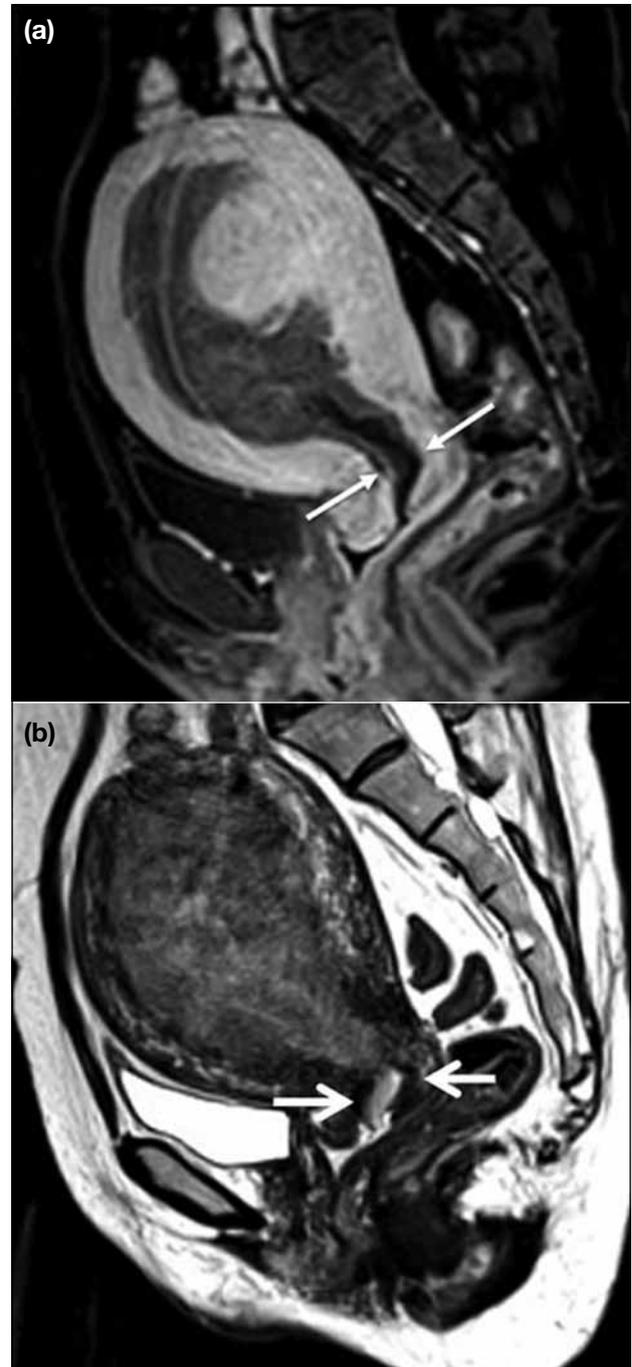


**Figure 3.** Cervical stromal invasion. Hypointense cervical stroma appears compressed but intact in (a) turbo spin echo T2-weighted image (arrow), but it is obviously breached in (b) high-resolution 3D T2-weighted image.

information bias than a prospective study. Besides, 1.5T MRI was used in our institution; the benefits of higher-field MRI cannot be excluded. Although Hori et al<sup>15</sup> advocate no added benefit of using 3T versus 1.5T MRI in staging endometrial cancer, this should be confirmed in future studies.

## CONCLUSIONS

Preoperative MRI is highly accurate in the prediction of



**Figure 4.** Histology-proven endometrial cancer with cervical stromal involvement. Sagittal (a) T1-weighted dynamic contrast-enhanced and (b) T2-weighted images showing very bulky tumour in endometrial cavity extending down to cervical canal with endocervical distension (arrows). The cervical stroma looks quite intact on both sequences. There may be very subtle tumour invasion of the upper cervical stroma that cannot be detected radiologically.

DMI, with high sensitivity and specificity. It is specific though not sensitive in the diagnosis of CSI and pelvic node metastasis. It allows better surgical planning and

therefore may translate into better patient outcome. Although not formally included in the FIGO staging system, staging MRI is a highly valuable adjunct in the preoperative assessment of women with endometrial cancer and should be advocated. Further studies may focus on the performance of high magnetic field (3T or above) multi-parametric MRI that holds great promise.

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