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RESEARCH

Evaluation of the Accuracy of Preoperative MRI in Measuring Myometrial Infiltration in Endometrial Carcinoma

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Abstract The aim of our study was to evaluate the diagnostic performance of magnetic resonance imaging (MRI) in the pretreatment evaluation of myometrium invasion in endometrial cancer. Our retrospective study concerns 89 patients with endometrial cancer, who had preoperative MR evaluation of myometrium invasion and we compared it with histological results. Considering histological type and grade, we had excluded patients with poor prognosis, and separately evaluated those cases where the depth of myometrium invasion is the main prognostic factor determining the choice treatment. Of the 89 cases MRI had accurately evaluated the depth of myometrial invasion in 75 patients. Based on data from all cases, we found the sensitivity of detection of deep myometrial infiltration by MRI (Sv) 71 %, specificity (Sp) 92 %, accuracy (Acc) 84 %, positive predictive value (PPV) 86 % and negative predictive value (NPV) 83 %. Excluding patients with poor prognosis according to histology and grade, these data were Sv 71 %, Sp 95 %, Acc 87 %, PPV 90 %, NPV 84 %. In conclusion, MRI is an efficient diagnostic tool in assessing myometrial infiltration, which is necessary for proper preoperative staging and therapy planning, including evaluation of the necessity of lymphadenectomy. Certain factors may interfere with evaluation of MRI results, thus hindering the precise determination of the level of myometrial infiltration.

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Introduction

Endometrial carcinoma (EC) is the most common gynaecological malignancy in developed countries. Its incidence is rising due to increased life expectancy and rise in obesity [1]. According to the American Cancer Society [2] the incidence of endometrial cancer had increased by 50 % in the US between 2000 and 2011 (31,000 new cases in 2000 and 46,470 new cases in 2011), and the annual number of patients who had died of endometrial cancer had increased by 25 %. Considering mortality, the Hungarian National Cancer Registry [3] reported that of all gynaecological cancers EC is second following ovarian cancer. Prolonged hormonal treatment, presence of hormone producing ovarian tumour, polycystic ovarian syndrome or prolonged tamoxifen treatment in the case of breast cancer patients increase the risk of EC [4]. EC is often preceded or accompanied by ovarian, breast or colon carcinoma.

The main prognostic factors determining the outcome of the disease and its treatment are histological type, pathological grade of differentiation and stage of the disease. The latter includes the depth of myometrial invasion, cervical involvement, and spread to the lymph nodes.

The incidence of lymph node metastases is directly proportional to the myometrial infiltration, thus the depth of myometrial invasion is one of the main prognostic factors influencing the therapy [5]. This information plays a crucial role in selecting high risk patients with possible lymph node metastases. In such cases, beside the usual hysterectomy and bilateral adnexectomy, pelvic and paraaortic lymph node dissections are also necessary.

According to the current protocol lymphadenectomy is carried out if the tumour is seropapillary or has clear cell histological type, has histological grade 3 or the myometrial

infiltration is more than 50 %. Histological type and grade is diagnosed from fractional curettage performed before the major surgery. Myometrial infiltration is determined non-invasively by MRI. The present study compares the preoperative interpretation of the MRI results of myometrial infiltration with the histological findings.

Materials and Methods

Patient Groups

Between 1 January, 2006 and 31 December, 2011, 89 EC patients were found who had MRI staging before surgery. Mean age was 59 years (range: 85–29 years). The majority of patients were between 50 and 70 years old (59 of 89). For statistical analysis a subgroup was created excluding Grade 3 patients or patients with clear cell and serous histology from all cases. This subgroup is called Group A later.

Surgical Protocol

According to the protocol applied in our Institute, every endometrial cancer patient undergoes surgery, unless it is contraindicated because of her comorbidities. The standard procedure is abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). Before surgery patients undergo imaging, in our institute we use MRI in all cases. The type of surgery and the need for lymphadenectomy depend on the MRI findings and the tumour status perceived during the operation. Since the Hungarian National Institute of Oncology is receiving many patients who had an imaging examination in other hospitals which is mostly CT scan, we have chosen only patients with preoperative MRI examination. All the patients included in the analysis were operated at the Hungarian National Institute of Oncology.

Methods and Evaluation of MRI

Every patient included in the study had MRI before surgery in the Hungarian National Institute of Oncology. MRI was performed with 1,5 T Siemens Symphony machine using high resolution surface coil. Before the scan patients were given buscopan, which helps to reduce artefacts from bowel peristalsis. Evaluation of pelvic lymph nodes, and organs was performed from the aorta bifurcation until the end of symphysis using T1-, T2-weighted and STIR axial plane measurements. Afterward, high resolution T2-weighted images were obtained sagittal, axial and perpendicular to the major uterine axis. After native series, contrast agent (Gd-DTPA) was given intravenously in every case and fat suppression measurements were performed in all three planes. The contrast sequences in sagittal plane were performed in 18 cases using dynamic contrast-enhanced MR (DCE-MR) [6].

During the MRI evaluation we have defined the position and the size of the uterus, extension of the tumour, myometrial infiltration and spread to the cervix. Invasion to the peritoneum, ovaries, surrounding tissues and pelvic lymph nodes were also evaluated. We have considered separately myometrial infiltration in T2-weighted and contrasted sequences. Benign uterine findings such as myoma, adenomyosis and endometritis were also considered.

Postsurgical Histopathological Examination

For final histology surgical materials were fixed in 8 % buffered formalin for 24 h. Intraoperative and postsurgical histological examinations were performed in accordance with the protocol of College of American Pathologists [7]. Sections of 5 μm thickness from paraffin-embedded blocks were stained with haematoxylin-eosin. Immunohistochemistry examination was carried out, when necessary, to determine histological type, myometrial infiltration or cervical involvement. Histopathological data contained all prognostic factors: histological type, differentiation grade, myometrial invasion in mm, the proportion of the invaded area to myometrium, the distance from serosa, blood vessel invasion, perineural invasion, cervical involvement, invasion

Table 1 Clinical and pathological details of tumours included in the study

Mean (range) age	59 (29–85)	
Tumour grade		
Unknown	1	1.1 %
I	36	40.4 %
II	42	47.2 %
III	10	11.2 %
Tumour type		
Endometrioid	81	91.0 %
Seropapillary	4	4.5 %
Adenosquamous	2	2.2 %
Clear cell	2	2.2 %
FIGO stage*		
IA	48	53.9 %
IB	24	27.0 %
II	9	10.1 %
IIIA	2	2.2 %
IIIB	0	0 %
IIIC	5	5.6 %
IV	1	1.1 %
Number of patients	89	100 %

*Full surgical staging was not performed in all cases

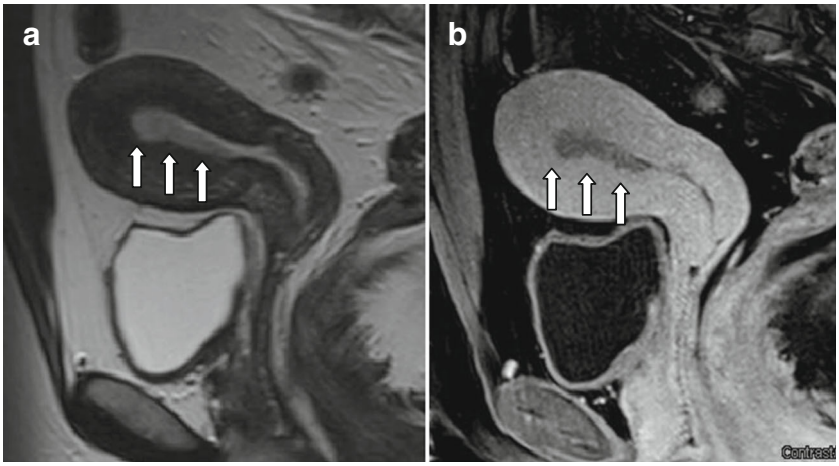

Fig. 1 (**a**) T2-weighted sagittal image. The tumour has intermediate signal intensity (*arrows*). (**b**) T1-weighted post-contrast fat-suppressed image. The tumour is hypoenhancing relative to the hyperenhancing myometrium (*arrows*), less than 50 % of the myometrium is infiltrated

of salpinx and ovaries, lymph node metastases, pathological TNM and FIGO staging [8].

Statistical Analysis

Data of myometrial infiltration obtained by MRI were compared with the histopathological results. Sensitivity, specificity, accuracy, negative and positive predictive values were calculated by Medical Statistics Made Easy [9] using SPSS for Windows 18.0.

Results

Out of 89 examined patients according to histology, two patients had clear cell carcinoma, four seropapillary carcinoma and two adenosquamous carcinoma, while the majority of patients (81 cases) had endometrioid type EC. In one case endometrial and cervical cancers were found simultaneously. Considering the differentiation grade, grade 1 was found in 36 cases, grade 2 in 42 cases and grade 3 in 10 cases. Of the 89 patients only one did not have a known grade, since the preoperative histology report did not contain grade and no tumour was found during postoperative histopathological examination (Table 1). Thirty-eight patients had lymphadenectomy and lymph node metastases were diagnosed by histology in four cases. Fifty-one patients did not have lymphadenectomy because it was unnecessary according to histological type and grade and/or depth of myometrial infiltration measured with MRI.

Endometrial cancer in T1-weighted MRI has the same intensity as myometrium and could not be defined. The normal zonal anatomy of uterus is easily detected by T2-weighted imaging. Generally, the normal endometrium has high intensity, while the tumour is mostly of intermediate signal intensity. In T2-weighted MRI myometrium has low intensity, the layer underneath the endometrium is the so called junction zone, which might be missing in post-menopause. Tumour infiltration is usually measured in T2-weighted MRI. Its accuracy can be improved by using contrast agents. In contrast measurement, the neoplastic tissue usually has low signal intensity, while the normal myometrium has high signal intensity. While measuring myometrial infiltration tumour's distance from serosa is compared to myometrial thickness.

According to MRI examination, 60 of 89 cases had myometrial infiltration of less than 50 % (Fig. 1). The

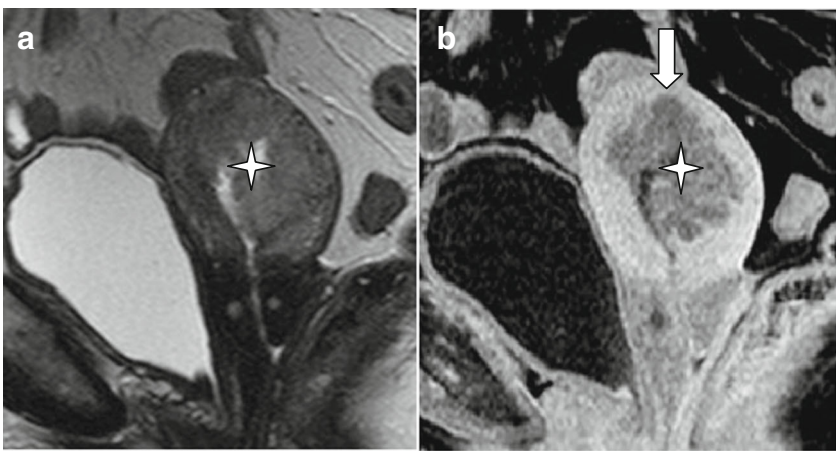

Fig. 2 T2-weighted (**a**) and T1-weighted post-contrast (**b**) sagittal MR images. The tumour (*star*) infiltrates more than 50 % of the myometrium (*arrow*)

Table 2 Myometrial infiltration, according to MRI examination and pathological results

	MRI	True MRI	False MRI	Pathology
<50 %	60	50	10	54
≥50 %	29	25	4	35
Total	89	75	14	89

following pathological examination had revealed myometrial infiltration to be less than 50 % in 50 cases, and more than 50 % in 10 cases. Therefore evaluation of myometrial infiltration by MRI was correct in 50 out of 60 cases. By MRI, 29 cases had myometrial infiltration of more than 50 % (Fig. 2), while histopathology showed that in four cases infiltration involved less than a half of the myometrium. In conclusion MRI evaluation of infiltration was correct in the remaining 25 cases (Table 2). Altogether, MRI had correctly diagnosed the myometrial infiltration in 75 of 89 cases.

According to the protocol applied in our institute, in case of grade 3, or histological type with poor prognosis (seropapillary or clear cell), lymphadenectomy should be performed in every case, regardless of the depth of myometrial invasion. However, depth of myometrial invasion is crucial in grade 1 and 2, and histological type with good prognosis (endometrioid carcinoma), thus we have studied data of such patients separately. Grade 3 was found in 10 cases, seropapillary tumour type was present in four cases, and clear cell tumour type was detected in two cases, in one case seropapillary tumour type was accompanied by grade 3, so 15 of 89 patients were excluded. Of the remaining 74 patients ("Group A"), 52 had myometrial infiltration of less than 50 % measured by MRI, which was confirmed by histology in 44 cases, and in eight cases the invasion was more than 50 %. MRI had shown myometrial invasion to be more than 50 % in 22 cases, which was confirmed by histology in 20 cases, while in two cases the myometrium was shown to be less than 50 % infiltrated (Table 3). Considering the data of Group A patients (74 cases), MRI had given correct diagnosis in 64 cases.

Data on comparison of histological findings with the MRI results, such as MRI sensitivity, specificity, NPV, PPV and accuracy are found in Table 4. Sensitivity of preoperative MRI in detection of deep myometrial invasion in both groups was

Table 3 The depth of myometrial infiltration according to MRI examination and pathological results; grade 3 and seropapillary or clear cell tumour types are excluded

	MRI	True MRI	False MRI	Pathology
<50 %	52	44	8	46
≥50 %	22	20	2	28
Total	74	64	10	74

Table 4 Comparison of preoperative MRI with pathological results concerning deep myometrial invasion. Statistic characteristics of the two groups, Group A (grade 3, seropapillary and clear cell types excluded) and Overall group (all patients included)

Category	Group A	Overall
Sensitivity	71 %	71 %
Specificity	95 %	92 %
PPV	90 %	86 %
NPV	84 %	83 %
Accuracy	87 %	84 %

71 %, specificity was high (in the overall group 92 %, and 95 % in Group A), PPV was 86 % and 90 % and NPV was 83 % and 84 %, respectively. The accuracy of MRI in the assessment of deep myometrial invasion was 84 % in overall group, and 87 % in Group A. Results of Group A were always better, especially PPV (4 % higher than in the overall group).

Besides endometrial tumour, other non malignant findings were detected in the uterus in 32 cases. Seventeen cases of myoma, 11 cases of adenomyosis, one polyp, one hyperplasia, one chronic endometritis and one endometriosis were found by histology. The above benign findings interfere with the MRI measurements of myometrial infiltration (Table 5), their influences are analysed in detail in the Discussion. Out of all benign findings, myoma and adenomyosis were the most common pitfalls hindering the evaluation of myometrial invasion.

Discussion

Endometrial cancer lymph node metastases are responsible for poor prognosis. The incidence of lymph node metastases depends on histological type, differentiation grade and depth of myometrial invasion. In case of lymph node metastases the risk of recurrence is six times higher, and 5-year survival is decreased from 85 % to 36 % [10]. Several working groups were conducting studies on large numbers of patients with EC, and have come to the conclusion that in early stage of the

Table 5 Benign pathological findings of all 89 patients

	Number of patients
Myoma	17
Adenomyosis	11
Polyp	1
Hyperplasia	1
Endometriosis	1
Chronic endometritis	1
Total	32

disease, lymphadenectomy does not improve overall survival [11, 12]. This is the reason why it is important to differentiate low-risk and high-risk patients, and in the latter group perform lymphadenectomy. EC is high-risk if it is clear cell or seropapillary histological type, differentiation grade 3 and/or myometrial infiltration is more than 50 %. EC is considered to be low-risk, with less possibility of recurrence, if it is endometrioid type, grade 1 and 2, and the depth of myometrial invasion is less than 50 %.

The depth of myometrial infiltration can be diagnosed non-invasively before surgery with imaging examination. According to numerous reports, MRI is the most appropriate imaging technique for the diagnosis of tumour spread within the uterus and for the evaluation of its invasion to the nearby tissues because of its excellent soft tissue resolution [13]. Preoperative MRI examination can help to decide the type of surgery and the need for lymphadenectomy.

The normal uterine zonal structure is well visible by T2-weighted imaging. Different uterine abnormities, benign or malignant tumours, such as EC, are well differentiated from normal myometrium on T2-weighted images. The application of contrast agent is especially important when the tumour and normal myometrium have similar signal intensity on T2-weighted images, or other factors, such as myoma or adenomyosis hinder the evaluation. For precise determination of myometrial invasion we have applied dynamic contrast-enhanced MRI (DCE-MRI) in 18 cases. The ESUR (Endometrial Cancer Staging Guidelines) also suggests DCE-MRI for examination protocol [14] although, according to others, DCE-MRI does not improve accuracy in comparison to non-dynamic MRI [15, 16].

Diffusion weighted imaging (DWI) is increasingly used for female pelvic examination, providing functional information and measuring the depth of myometrial invasion. It has been suggested that DWI might substitute contrast agent dynamic examination beside T1- and T2-weighted imaging [17]. DWI can be used for detecting tumour spread beyond the uterus, peritoneal and lymph node metastases. It was not possible to apply DWI technique for the mentioned 89 patients, but since the recent installation of the machine, DWI has become a part of our examination protocol.

Table 6 Comparison of sensitivity and specificity of MRI for deep myometrial invasion as shown in different studies

Study	Sensitivity (%)	Specificity (%)	Total number of patients
Nakao et al 2006 [18]	75	93	116
Chung et al 2007 [16]	51	89	120
Ortashi et al 2008 [19]	56	86	100
Hwang et al 2009 [20]	50	90	53
Emlik et al 2010 [21]	76	75	53
McComiskey et al 2012 [22]	73	83	183
Present study	71	92	89

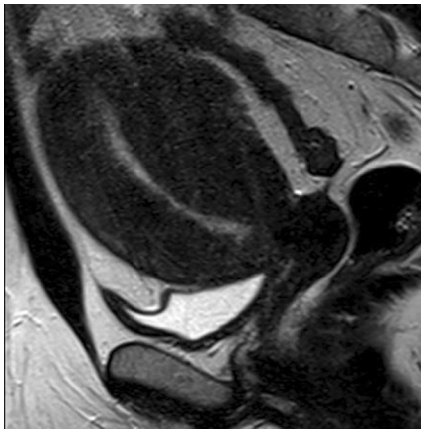

Fig. 3 T2-weighted sagittal MR image. The myometrium is infiltrated by endometriosis, and the tumour cannot be distinguished

According to our study on 89 patients, deep myometrial infiltration was detected by MRI with 71 % sensitivity and 92 % specificity. Studying the recent literature, other authors have reported similar results (Table 6). Considering the results of Group A (excluding grade 3, seropapillary and clear cell type cases) where the main factor for lymphadenectomy is deep myometrial invasion, sensitivity was 71 % as well, but specificity was 95 %. PPV and NPV were 90 % and 84 %, respectively, which are better than in the overall group. Measurement of myometrial infiltration by MRI, which is the most important prognostic factor in Group A, had 87 % accuracy.

MRI determined the depth of myometrial invasion correctly in 75 of 89 cases and incorrectly in 14 cases. It had detected myometrial infiltration of less than 50 % in 60 cases, which was incorrect in 10 cases (17 %), in comparison to the

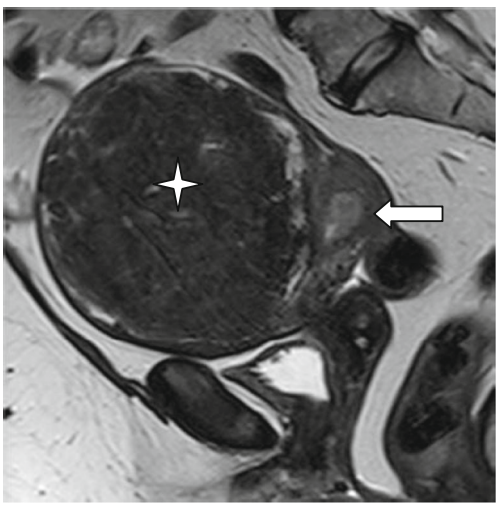

Fig. 4 T2-weighted sagittal MR image. Large intramural myoma with low signal intensity (*star*); the EC infiltrates more than 50 % of the myometrium (*arrow*) histologicaly

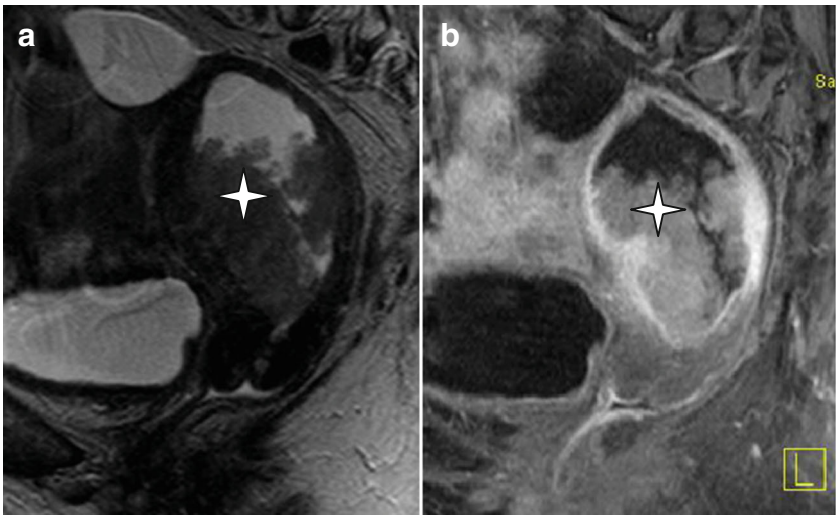

Fig. 5 T2-weighted (**a**) and T1-weighted contrast-enhanced, fat-suppressed (**b**) sagittal MR image of seropapillary tumour. The myometrium is significantly thinner because of the uterine cavity being filled by seropapillary tumour (*stars*). According to MRI deep myometrial infiltration was supposed, but the pathological results revealed superficial myometrial infiltration

pathological findings. MRI had diagnosed myometrial infiltration to be more than 50 % in 29 cases, which was overestimated in 4 cases (14 %). In some of the incorrectly evaluated cases the tumour could not be differentiated from the myometrium on T2-weighted images because of diffuse adenomyosis (Fig. 3) or endometritis. In some cases myometrium was significantly thinner because of large myoma (Fig. 4) or endometrial cavity filled with papillary

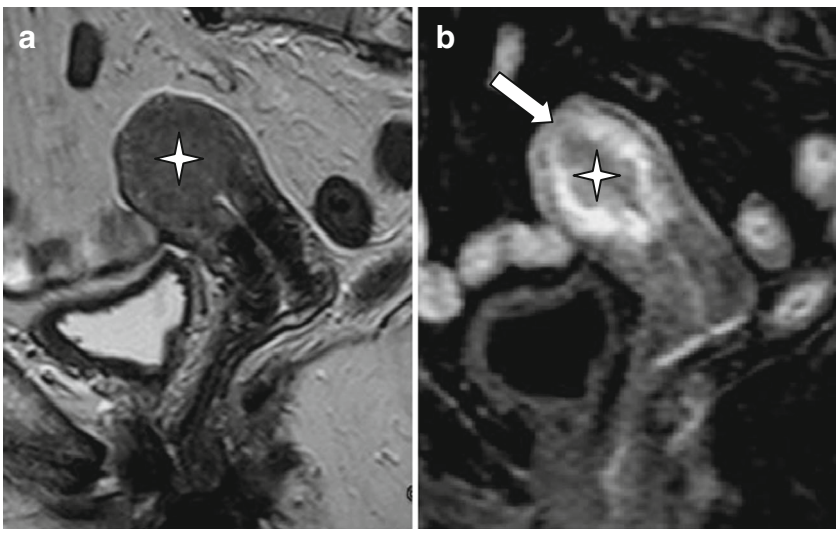

Fig. 6 (**a**) T2-weighted sagittal MR image. The tumour (*star*) has almost the same intensity as the myometrium. (**b**) In the early phase of dynamic contrast-enchanced fat-suppressed MRI, the myometrium is hyperenhancing relative to the tumour (*star*), so the border between them is clearly defined (*arrow*). At the fundus the tumour has infiltrated more than 50 % of the myometrium

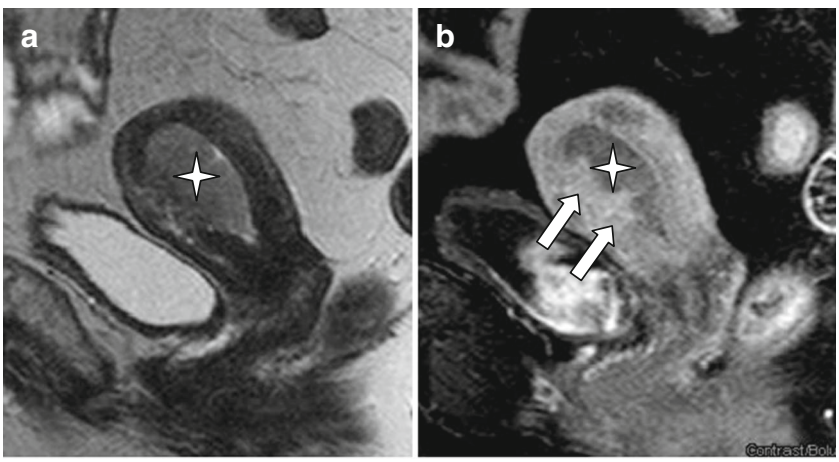

Fig. 7 (**a**) T2-weighted sagittal MR image. A part of the tumour (*star*) has almost the same intensity as the myometrium. (**b**) T1-weighted fat-suppressed image. A polypoid component of the tumour protruding in the uterine cavity (*star*) shows low intesity but its "stem" infiltrating the myometrium is hyperenhancing similarly to the myometrium so the depth of invasion cannot be defined (*arrow*)

tumour (Fig. 5), which made evaluation of myometrial invasion difficult. In one case the tumour had almost the same intensity as normal myometrium on the T2-weighted measurement, so DCE-MRI was performed, which made it possible to differentiate the tumour from the myometrium by their contrast enhancement (Fig. 6). Another possible pitfall was when the tumour (or part of it) and the myometrium have shown similarly high intensity on post-contrast images and T2-weighted images was not suitable for evaluation of myometrial invasion either (Fig. 7). Considering the anatomical structure of the normal uterus, myometrium thickness is different in parts of the uterus (for example fundus and corner of the uterus), which makes it difficult to measure its thickness.

Conclusion

The preoperative evaluation of EC myometrial infiltration is very important since it helps to differentiate between high- and low-risk patients, and provides the necessary information for the surgeon to determine the need for lymphadenectomy.

The depth of myometrial invasion is the main prognostic factor in most cases. For its non-invasive examination MRI is the most suitable imaging technique, because it has high soft tissue resolution so the structure of the uterus, tumour and non-tumour lesions can easily be differentiated. Preoperative MRI is efficient in measuring myometrial invasion and staging EC, assisting treatment planning, although, in spite of the best techniques, there can be pitfalls which may make accurate evaluation difficult. For example, papillary tumour type leads to thinning of myometrium or tumour and normal myometrium also have high signal intensity on post-contrast images. Benign uterine lesions, such as myoma, adenomyosis, or endometritis hinder the evaluation as well.

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