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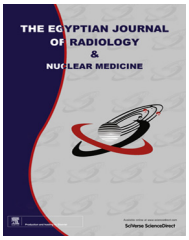

ORIGINAL ARTICLE

Can dynamic contrast enhanced magnetic resonance imaging change treatment planning in endometrial carcinoma?

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KEYWORDS

Endometrial cancer;
Dynamic magnetic resonance imaging;
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Abstract *Purpose:* To detect the diagnostic accuracy of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) in the assessment of myometrium and cervix infiltration and lymph node (L.N) status in patients with endometrial carcinoma.

Patients and methods: Forty patients with pathologically proven endometrial carcinoma underwent preoperative MRI assessment in the National Cancer Institute, Cairo University, Egypt over three years from 2009 to 2012. Every case had one stage for the T2 weighted images (T2 WIs) alone and another stage for the combined T2 and DCE images according to the revised international federation of gynecology and obstetrics (FIGO) classification. The pathological findings after surgery were the reference standard.

Results: The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of T2 WIs in detection of deep myometrial invasion were 80%, 72%, 70%, 84% and 79%, respectively and 87%, 90%, 85%, 92% and 87%, respectively for DCE-MRI. For cervical infiltration, T2 WIs showed 78.5%, 88%, 73%, 90.5% and 82.5%, respectively while DCE-MRI showed 92%, 97%, 92%, 97% and 95%, respectively. T2 WIs and DCE-MRI had 100% sensitivity and 85% specificity for the detection of L.N metastasis.

Conclusion: DCE-MRI can accurately detect invasion of the myometrium and cervix in cases of endometrial carcinoma.

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1. Introduction

Endometrial carcinoma is the fourth most common cancer in females and the most common malignancy of the female reproductive tract (1).

Treatment planning of patients with endometrial carcinoma depends on accurate staging of the disease, nodal status and the histologic grade (2) as stages higher than the stage I (who are treated by total hysterectomy and bilateral salpingo-oophorectomy) need additional treatment in the form of lymph node dissection and adjuvant radiotherapy (3).

Extension of the tumor into the myometrium is probably the single most important morphologic prognostic factor as it correlates with tumor grade, tumor extension into the cervix and the prevalence of lymph node metastases as incidence of lymph node metastases increases from 3% with stage IB to 46% with stage IC (4).

The presence and depth of cervical infiltration also affect the prognosis and management of endometrial carcinoma (5).

The presence of myometrial invasion greater than 50% or the presence of a large tumor (>2 cm in diameter or filling the endometrial cavity) indicates a high risk of nodal disease, even in apparent stage I disease; therefore, the presence of any of these features suggests the benefit from surgical resection of the lymph nodes (6).

The evaluation of the extent of myometrial invasion by gross inspection at surgery or at frozen section remains inaccurate in a significant proportion of patients (7).

Although MRI is not formally incorporated into the revised FIGO staging system (Table 1) (8), it is widely used by clinicians to assess the stage of the disease in both endometrial and cervical cancers (9). However, there is no certain technique in the literature regarding the best MRI protocol in gynecological tumors which is considered worldwide accepted (10,11).

The aims of this study were to evaluate the accuracy of DCE-MRI in the identification of myometrial and cervical stromal invasion and lymph node status in cases of endometrial carcinoma.

2. Patients and methods

Forty patients with pathologically proven primary endometrial carcinoma were included in this study. The age of the patients ranged from 39 to 78 years (with mean age 59). All patients underwent preoperative assessment with dynamic MRI study of the pelvis and lower abdomen.

MRI examinations were done with 1.5 Tesla MRI machine (GE machine, USA) using phased-array pelvic coils in a supine position with partially full urinary bladder. An antiperistaltic agent such as buscopan (20 mg butylscopolamine) was administered intramuscularly before the examination to reduce artifacts from the small bowel peristalsis. Each examination included precontrast, high resolution Fast Recovery Fast Spin Echo (FRFSE) sequences for better tumor delineation using T2W sagittal, axial, and axial oblique planes, and T1W axial sequences of the pelvis and lower abdomen. All axial oblique images are obtained in a plane perpendicular to the endometrial cavity (12). Dynamic contrast enhanced MRI after administration of 0.1 mmol of gadolinium per kilogram body weight (pump injection) was performed by using the multiphase technique (sagittal and axial oblique before contrast and at 25 s, 1 min, and 2 min in the sagittal plane and at 4 min in the axial oblique plane after contrast). Axial images of the lower abdomen were also done to detect lymphadenopathy using axial fast imaging employing steady-state acquisition. Imaging parameters were as follows: repetition time/echo time, 3.6:1.75 ms; number of excitations, 0.75; matrix, 288_192; field of view, 36 cm; section thickness, 4 mm interpolated to 2 mm.

2.1. Image interpretation

MR images were analyzed without knowing the final histopathology results at the time of examination. The MR images were evaluated independently by two radiologists (A.M and Y.M); disagreement was resolved by joint reevaluation.

The unenhanced images (T1 and T2 WIs) were evaluated initially and staging was assigned for each case. An identical scoring system was used to evaluate the DCE-MRI according to the revised FIGO staging system.

In T2 WIs, no myometrial infiltration was considered when the junctional zone (JZ) was intact and the tumor is confined to the endometrium. Superficial myometrial infiltration was considered when focal disruption of the JZ was present while complete disruption of the JZ indicated deep myometrial infiltration. The junctional zone on T2 WIs appears as a band of low signal intensity immediately subjacent to the endometrial stripe.

Table 1 Revised FIGO staging of endometrial carcinoma.

Stage I	Confined to corpus
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrial invasion
Stage II	Tumor invades cervical stroma, but does not extend beyond the uterus
Stage III	Local and/or regional spread of the tumor
IIIA	Invasion of serosa, adnexa, or positive peritoneal cytology
IIIB	Invasion of vagina and/or parametrial involvement
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic nodes with or without positive pelvic nodes
Stage IV	Tumor invades bladder and/ or bowel mucosa, and/or distant metastases
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

In post menopausal women, there is thinning of the myometrium secondary to uterine involution, which could make accurate assessment of the depth of myometrial invasion challenging at conventional MR imaging (12).

Intact subendometrial enhancement (SEE) band on DCE-MRI indicates no myometrial invasion. In cases where the SEE band was not visible, a smooth tumor-to-myometrium interface indicated a tumor confined to the endometrium. Superficial myometrial invasion was diagnosed when the SEE was interrupted or the interface between the tumor and the myometrium was irregular, with low signal intensity tumor involving less than 50% of myometrial thickness. Extension of the tumor beyond 50% of myometrium thickness indicated deep myometrial invasion.

Regarding cervical infiltration, abnormal signal intensity on T2 WIs extending into the cervical canal or stroma or widening of the cervical canal was considered cervical involvement. On DCE-MRI, disruption of cervical epithelium enhancement was considered cervical involvement.

In T2 WIs, lymph nodes show intermediate signal intensity compared to the adjacent hypointense blood vessels. Necrosis appears as an area of low signal intensity. In the post contrast images, normal lymph nodes show homogenous enhancement and areas of necrosis appear as non enhancing areas.

2.2. Surgical analysis

Total hysterectomy with bilateral salpingo-oophorectomy and lymph node dissection is the standard staging procedure for endometrial carcinoma. Vaginal, laparoscopic or robot-assisted approaches are also possible nowadays (13).

As with other abdominal gynecologic malignancies; complete staging of endometrial carcinoma includes biopsy of any area where metastases are suspected. Pelvic and para-aortic lymph node sampling is done selectively (14).

Vaginal hysterectomy is not recommended for endometrial carcinoma staging since it precludes examination of the abdomen and lymph nodes for metastases. However, it is performed for women who are poor candidates for surgery (15,16).

Lymph node dissection was done with anatomic labeling into each group. The total number of metastatic lymph nodes was documented by the pathologist.

2.3. Statistical analysis

The sensitivity, specificity, PPV, NPV, and overall diagnostic accuracy for the T2W images alone and combined T2WI and DCE-MRI were calculated. The hypothesis of no disproportionate change between assessments (i.e., correct, incorrect assessments) made using the T2WI alone and combined T2WI and DCE-MRI method was tested using the McNemar test. Associations between assessment of depth of myometrial invasion and possible pitfalls previously mentioned on T2W images were examined by implementing Fisher exact test. PG 0.05 was considered statistically significant. All analyses were performed using SPSS Version 14 and Stat-Exact 4.

3. Results

Endometrial cancer is isointense relative to the hypointense normal endometrium on unenhanced T1 WIs. On T2 WIs; it most commonly shows heterogeneous intermediate signal intensity relative to the hyperintense normal endometrium and mildly hyperintense relative to the normal myometrium (17).

Endometrial tumors enhance earlier than does the normal endometrium after administration of intravenous contrast medium (CM), which aids in the detection of small tumors confined to the endometrial complex. Normal myometrium enhances intensely compared with hypointense endometrial tumor. Maximum contrast between hyperintense myometrium and hypointense endometrial tumor occurs 50–120 s after CM administration, and this is the most important phase for accurate assessment of the depth of myometrial invasion (18) (Fig. 1). Delayed-phase images obtained 3–4 min after CM administration are useful in the evaluation of cervical stromal invasion (Fig. 2). The presence of an intact enhancing cervical mucosa excludes stromal invasion. The cervical epithelium normally shows a significant enhancement more than the tumor (8).

In our study, total hysterectomy and bilateral salpingo-oophorectomy were done in all cases. 15 patients (37.5%) underwent open total abdominal hysterectomy (TAH) and 25 patients (62.5%) underwent laparoscopic approach. Eight out of 40 patients (20%) underwent lymph node sampling while 13 cases (32.5%) underwent pelvic and aortic lymphadenectomy. This decision was based on the presence of an extra-uterine disease and possible lymph node involvement on MR studies.

The surgical specimens were examined pathologically by specialized pathologists to detect the depth of myometrial invasion, the presence of cervical stroma invasion and the presence of metastasis within the sampled lymph nodes.

3.1. Myometrial infiltration

Regarding the depth of myometrial infiltration, agreement between T2 WIs and pathology was found in 31/40 patients (77.5%) while agreement between DCE-MRI and pathology was found in 38/40 patients (95%). The sensitivity, specificity, PPV, NPV and diagnostic accuracy of T2 WIs in the detection of deep myometrial invasion were 80%, 72%, 70%, 84% and 79%, respectively and 87%, 90%, 85%, 92% and 87%, respectively for the DCE-MR images (Figs. 3 and 4). Of note, the addition of DCE-MRI led to a correct detection of deep myometrial invasion in all cases.

The diagnostic performance of T2 WIs and DCE-MRI in the assessment of depth of myometrial invasion is shown in Table 2.

3.2. Cervical infiltration

T2 WIs showed sensitivity of 78.5%, specificity of 88%, PPV of 73%, NPV of 90.5% and diagnostic accuracy of 82.5% while DCE-MRI showed 92% sensitivity, 97% specificity, 92% PPV, 97% NPV and 95% diagnostic accuracy (Table 3).

11 out of 40 patients (27.5%) had pathologically proven cervical stromal invasion. T2 WIs could correctly diagnose 8 out of these 11 cases with 3 false-negative diagnoses. Of the 29 patients (72.5%) without histologic diagnosis of cervical involvement, a false-positive diagnosis was made with T2 WIs in 4 patients. DCE-MRI could correctly diagnose 10

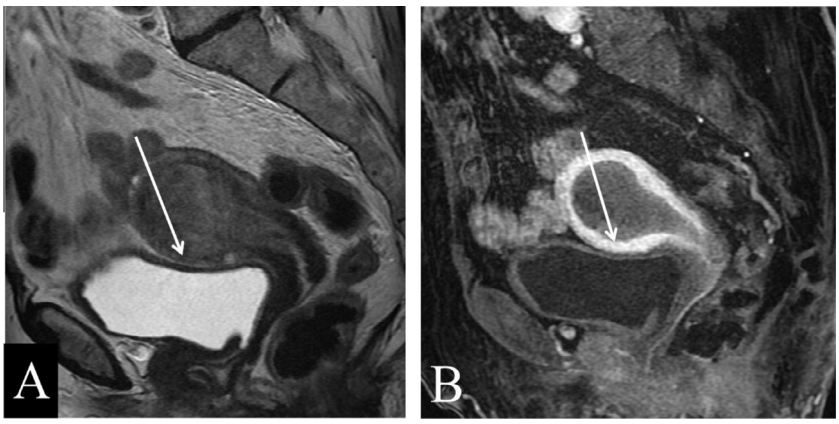

Fig. 1 Sagittal T2W FRFSE (A) shows an endometrial carcinoma in a 90-year-old woman presenting with vaginal bleeding. There is a poor tumor-to-myometrium contrast especially anteriorly (arrow) leading to an overestimation of depth of myometrial invasion on T2WI only (deep invasion) especially in the presence of thin myometrium secondary to uterine involution. Sagittal gadolinium-enhanced fat-suppressed T1WIs FSPGR (B) demonstrate superficial myometrial invasion by the tumor (arrow) which was confirmed histologically.

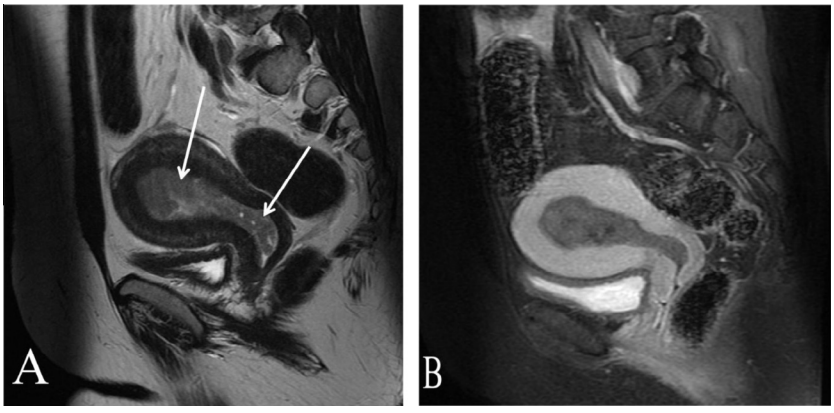

Fig. 2 Sagittal T2W FRFSE (A) shows an endometrial carcinoma in a 36-year-old woman presenting with vaginal bleeding. The tumor fills the endometrial cavity with superficial invasion of the myometrium and extends into the cervical canal (arrows). Sagittal gadolinium-enhanced fat-suppressed T1WI FSPGR (B) confirms the superficial myometrial invasion and cervical extension which were confirmed surgically.

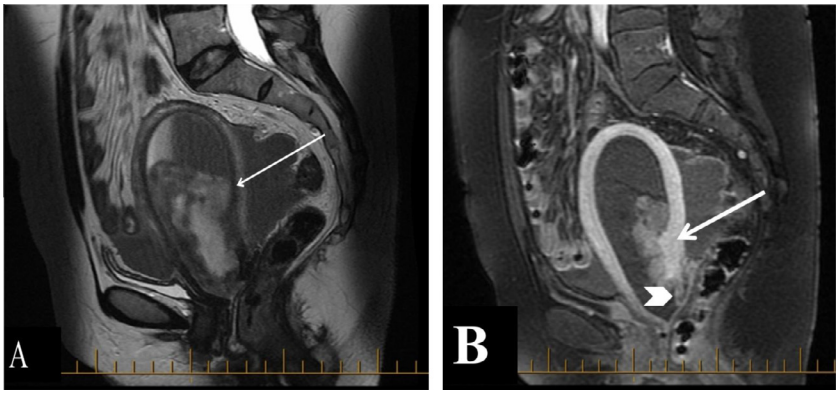

Fig. 3 Sagittal T2W FRFSE (A) shows polypoidal endometrial carcinoma in a 61-year-old woman with poor tumor-to-myometrium contrast especially posteriorly (arrows) leading to an overestimation of depth of myometrial invasion on T2WI alone (thought to be superficial myometrial invasion) and no clear cervical extension. The sagittal gadolinium-enhanced T1W fat-suppressed MR image (B) demonstrates a well defined tumor-to-myometrium interface (arrow) indicating no myometrial invasion with extension of the tumor into the endocervix (arrowhead) which were confirmed at the final histologic finding.

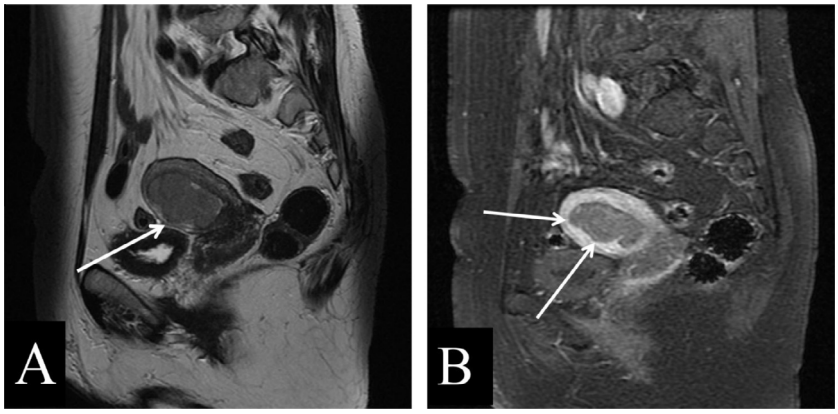

Fig. 4 Sagittal T2W FRFSE (A) shows an endometrial carcinoma in a 78-year-old woman presenting with vaginal bleeding and deep myometrial infiltration anteriorly. The dynamic contrast enhanced image (B) demonstrates superficial myometrial invasion superiorly and anteriorly (arrows) which was confirmed at the final histologic finding.

Table 2 Number and percentage of patients correctly identified radiologically with myometrial invasion compared with surgicopathological findings.

MR Finding	T2W	DCE
No myometrial invasion	57 (4/7)	85.7 (6/7)
< 50% myometrial invasion	82.6 (19/23)	95.6 (22/23)
> 50% myometrial invasion	80.0 (8/10)	100.0 (10/10)

Table 3 Percentage of Cervical Involvement by the MRI techniques.

MRI Technique	Sensitivity	Specificity	PPV	NPV	Accuracy
T2 WIs	78.5	88	73	90.5	82.5
DCE-MRI	92	97	92	97	95

out of the 11 cases (91%) as one case was missed as she had tumor extension beyond the internal os microscopically. One out of 29 patients without cervical infiltration was misdiagnosed as a false positive case which could be due to the presence of large cervical polyp which was misdiagnosed as tumor extension.

3.3. Lymph node

The MRI showed 100% sensitivity and 85% specificity for both T2WIs and DCE-MRI in detecting lymph node metastasis. MR imaging assessment of lymph node status resulted in one (4.7%) of 21 patients with true-positive, 18 (85.7%) of 21 patients with true-negative, one (4.7%) of 21 patients with false-positive, and one (4.7%) of 21 patients with false-negative findings.

4. Discussion

The histological grade and the stage of endometrial carcinoma can predict the occurrence of extra uterine spread and lymph node metastases (19,4,20). It can also affect the prognosis and treatment as patients with early stage disease need in most of the cases minimally invasive surgery such as simple hysterectomy while patients at high risk of extra uterine disease or nodal metastases (grade 3, deep myometrial and/or cervical infiltration), will benefit from lymphadenectomy and preoperative or postoperative radiation therapy (3,21–23).

Staging of endometrial tumors is usually done surgically, but MRI is now widely used as a non-invasive imaging modality in predicting myometrial and cervical invasion and to detect lymph node involvement (24).

Although MRI is now widely used for preoperative staging of endometrial carcinoma, there is still no certain imaging protocol which is universally accepted (10,25,11).

In our study, we try to detect the usefulness of DCE-MRI in the accurate evaluation of depth of myometrial infiltration and cervical stromal involvement in cases of endometrial carcinoma.

Our results showed that the addition of DCE-MRI to the T2WIs resulted in a significant improvement in the accuracy of assessment of deep myometrial invasion and cervical stromal invasion and lymph node enlargement.

In addition, DCE-MRI led to a correct identification of deep myometrial invasion in all cases. These results were very close to those found by Sala et al., (2) but were different from those done by Rockall et al., (25) in which the dynamic enhancement did not improve the diagnostic performance in 84 patients. However, this study was done over a 10-year period, and during this time MRI technology and protocols improved significantly. Our results were very close to those found by Sala et al., (2) probably because it was recently done, so they used nearly the same protocol and the same machine as we used. Their study showed 91.4% sensitivity, 80% specificity, 91.4% PPV and 80% NPV of T2WIs in accurate detection of depth of myometrial invasion increasing to 97.1% sensitivity, 100% specificity, 100% PPV and 93.7% NPV for combined T2 and DCE T1 WIs.

Zandrino et al., (5) results also proved the usefulness of DCE-MRI in cases of endometrial tumors in which T2 WIs showed sensitivity of 85%, specificity of 76%, PPV of 73% and NVP of 87% in accurate detection of depth of myometrial invasion while post contrast T1WIs showed sensitivity of 90%, specificity of 80%, PPV of 82% and NPV of 89%.

The same results found by Rockall et al., (25) were also found by Chung et al., (9) in which administration of gadolinium did not distinguish myometrial invasion of tumor from normal myometrium in a subset of 24 patient study. But again, their study was done over a 9 year period where changes in the technique and practice may have had an effect and the study was done in a small number of patients.

Some other authors did not find significant differences between non-contrast and contrast-enhanced MRI especially when high-resolution T2 WIs was used (26,27).

On the other hand, many researches other than those done by Sala et al., (2) supported the routine use of dynamic IV contrast enhancement to improve the accuracy of assessment of depth of myometrial invasion (accuracy of 55–77% for T2WIs vs 85–91% for DCE-MRI) (11,25,28). In a recent prospective study, Manfredi et al., (10) showed the importance of dynamic MRI as it allows detection of different enhancement times of the endometrial tumor compared with the adjacent normal myometrium.

Many other papers reported a better diagnostic performance of DCE-MRI (accuracy 85–95% vs 58–78%) (24,29,30).

The addition of DCE-MRI could clearly differentiate the intensely enhancing normal myometrium from the relatively poorly enhancing tumor.

In our study, the JZ was found to be a useful landmark for determining the presence or absence of myometrial invasion. The JZ was present in most of our patients [35 out of 40] unlike other authors in which the JZ was not present in most of their cases (17,18). Chung et al., (9) also found that the JZ was preserved in most of their patients regardless of the menopausal status, but they did not find it useful in assessing deep myometrial invasion.

On T2 WIs, the relationship between the tumor and the JZ is highly predictive of deep myometrial infiltration (5). Unfortunately, in post menopausal patients, patients with large endometrial tumors, multiple or large leiomyomas, small or retroverted uterus, uterus with congenital anomalies or cases of adenomyosis, the zonal anatomy may be difficult to identify and overstaging or understaging may occur (20,23,24,31,32).

In the 9 cases of staging error on T2 WIs in our study, 3 patients were post menopausal but the rest of the cases had normal uterine morphology and no abnormalities found at pathological examination.

DCE-MRI is more helpful than T2WIs in cases of thickened or ill defined junctional zone as it allows a clear differentiation between the tumor, endometrium and myometrium. It is also more helpful in cases of large tumors causing thinning of the myometrium.

MRI was also found to be very accurate in the detection of cervical stromal invasion. This is similar to the results found by Manfredi et al., (10), Seki et al., (33) and Nagar et al., (34) which showed the accuracy of MRI in detecting cervical stromal invasion reaching 92% with sensitivities of 75–84% and specificities of 94–96%.

Some authors reported that T2WIs seem to have a better diagnostic performance than contrast-enhanced sequences. T2WIs can discriminate hyperintense tumor disrupting low-signal-intensity cervical stroma while, after contrast, tumor and stroma may have a similar enhancement. However; contrast agent may be useful to differentiate tumor from endocervical debris and to detect the lesion in cases of superficial infiltration, when hyperintense tumor and epithelium cannot be discriminated on T2WIs (23).

False positive results in DCE-MRI could occur in cases of chronic cervicitis.

Our study showed higher specificity and positive predictive value for assessing cervical involvement with DCE-MRI than T2 WIs as the former can detect the continuity of enhancing cervical epithelium which excludes cervical infiltration as false-positive cases of cervical infiltration in T2WIs caused by a dilated cervical canal without cervical involvement. In most cases, enhancement of the cervical epithelium was greater than that of the tumor and cervical stroma especially, in phase 2 or 3 of the dynamic MR imaging.

In our study, only patients with MR evidence of lymph node enlargement underwent lymphadenectomy which led to an overestimation of the accuracy of MRI in predicting lymph node metastases.

The limitation of MRI in the assessment of lymph node metastasis is that it depends on the size of the lymph nodes using 1 cm as a cutoff value or the presence of areas of central necrosis. Some metastatic lymph nodes are less than 1 cm leading to false negative results while others proved to be non metastatic although they were larger than 1 cm leading to false positive results. Some metastatic lymph nodes do not show necrosis whatever the size of the node.

5. Conclusion

DCE-MRI can significantly increase the accuracy of MRI in the assessment of depth of myometrial infiltration and cervical invasion in cases of endometrial carcinoma and may be a useful tool to guide the surgical approach in these cases and select patients which will benefit from neoadjuvant chemotherapy or radiation therapy. DCE-MRI adds only about 4 min to the total time of the study.

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