The Added Role of Diffusion Weighted Imaging in the Staging of Endometrial Carcinoma

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Abstract

Objective: To assess the value of Diffusion Weighted Imaging (DWI) versus Dynamic Contrast Enhanced MRI (DCE-MRI) in the staging of endometrial carcinoma.

Methodology: Twenty five cases of pathologically proved endometrial cancer prior staging subjected to dynamic post contrast technique: One pre-and six post contrast phases (40sec. each). DWI was scanned using different p-values, ADC values were measured and fusion images (T2/DWI) were automatically generated.

Results: DWI was the most accurate in overall staging (93.3%). Deep myometrial invasion was overestimated in 1 case in both DWI and DCE-MRI versus 3 cases in conventional MR imaging. In assessment of cervical stromal invasion, they all perform equally with overestimation in only 1 case. DWI is the modality of choice for assessment of locally advanced carcinomas; sensitivity, positive predictive value and accuracy of 100%. In metastatic lymph nodes, DCE-MR showed the least accuracy of 86%.

Conclusion: DWI (with fusion images) is valuable in overall staging of endometrial cancer owing to its superiority in evaluation of locally advanced disease and metastatic deposits. DCE-MR can delineate local tumors and exclude bladder/rectal invasion.


Introduction

ENDOMETRIAL cancer, being the sixth most common cancer in women worldwide, is considered the most important gynecological malignancy, being more common in the developed countries [1].

Staging of endometrial cancer is surgical based on the International Federation of Gynecology and Obstetrics (FIGO) surgical-pathologic staging system, revised in 2009 [2]. The incidence of lymph node metastases is greatly dependent on the depth of myometrial invasion which in return can predict the recurrence risk and overall survival. However; the integration of lymphadenectomy in routine surgical staging remains controversial [3].

Non-invasive MR imaging is valuable in the preoperative evaluation of important prognostic factors and accordingly, can allow taking the proper decision on the surgical approach in advance as well as planning preoperative chemotherapy or radiation therapy if needed [4].

Due to limitations of morphologic imaging as in lesion characterization, accurate lymph node staging, assessment of tumour response and inability to differentiate post-treatment changes from tumour recurrence, functional imaging is becoming part of the standard imaging protocols for evaluation of the female pelvis [5].

Accordingly, the European Society for Urological Research has recommended the combination of dynamic contrast-enhanced and T2-weighted MR imaging in its guidelines for endometrial cancer staging [6]. It aids in detecting small tumors confined to the endometrial cavity, assessing the depth of myometrial invasion especially in the presence of reported pitfalls as leiomyomas and adenomyosis, as well as detection of cervical stromal invasion [7].

The other functional imaging technique is Diffusion-Weighted MR imaging (DWI) that allows clear depiction of endometrial tumors [7]. Fusion images can combine the unique functional information of DWI or ADC map with the anatomical details provided by the morphologic T1-or T2-weighted sequences and thus can improve the staging accuracy [8].
The purpose of this study was to compare the diagnostic performance of DWI with that of DCE MR imaging in the evaluation of the overall stage in patients with endometrial cancer and if it can replace it as a one stop imaging modality when combined with conventional imaging.

**Patients and Methods**

The current work is a prospective analysis approved by the Ethics Committee of the Faculty of Medicine, Cairo University and cases had been supplied by Kasr Al-Ainy Hospital. Included patients gave informed consent. The patients were referred from the Gynecology Department with the diagnosis of endometrial cancer after initial biopsy confirmation for pre-management staging to the Radiology Department in the period from February 2012 to April 2015.

DWI in addition to the routine pelvic MRI protocol was done to 50 female patients with pathologically proved cervical carcinoma. All cases were subjected to the following protocol:

- Full history taking with a special emphasis on: Age, parity, history of replacement hormonal or contraceptive therapy, previous gynecological problem or curettage.
- Routine laboratory investigation for all patients.

MR imaging was performed on a 1.5-Tesla MR scanner (Gyroscan Entra, and Achieva) Philips medical systems.

All the patients were imaged in the supine position using pelvic phased-array coil.

**Protocol of MR imaging:**

The used protocol for optimum evaluation of endometrial cancer is emphasized on (Table 1).

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Plan</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T₁ weighted.</strong></td>
<td>Axial.</td>
<td>• Evaluate bone marrow and lymph nodes.</td>
</tr>
<tr>
<td><strong>T₂-weighted.</strong></td>
<td>Axial oblique (perpendicular to the endometrium), sagittal and coronal.</td>
<td>• Visualize tumor and evaluate depth of myometrial invasion.</td>
</tr>
<tr>
<td><strong>DCE-MRI (T₁ THRIVE; high resolution isotropic volume examination).</strong></td>
<td>Axial oblique at 0, 40, 60, and 120 and 240sec.</td>
<td>• Assess cervical extension. • Evaluate lymph nodes.</td>
</tr>
<tr>
<td><strong>DW-MRI.</strong></td>
<td>Axial oblique. Fused T₂/DWI</td>
<td>• Tumor characterization and its local extent.</td>
</tr>
</tbody>
</table>

**Image analysis:**

MR image interpretation was performed by two consultants of radiology who were blinded about each other imaging as well as to the post operative histopathologic reports.

Each reader evaluated the standard anatomic sequences (T₁-and T₂-weighted imaging), DW MR images and DCE-MR images for the following findings:

- Tumor signal intensity on T₁-, T₂-weighted images and DW MR images compared with that of adjacent myometrium.
- Visibility of the junctional zone on T₂-weighted images as a band of low signal intensity immediately subjacent to the endometrial stripe.
- Depth of myometrial invasion.
  - Less than 50% (superficial myometrial invasion).
  - Greater than 50% (deep myometrial invasion).
- Presence of cervical stromal invasion (detected by disruption of the hypointense cervical stroma).
- Adnexal extension.
- Vaginal or other pelvic organ invasion.
- Presence of enlarged pelvic and/or para-aortic lymph nodes (cut off value, 10mm along the minimal transverse diameter as well as restricted diffusion with low ADC in DW MR images).
- ADC measurement of the tumor and the suspected enlarged lymph nodes on ADC map.
- Metastatic disease.

Statistical analysis:
- Computer software package SPSS (Version 12 windows) was used in the analysis.
- Results are expressed as mean (as a measure of central tendency) ± standard deviation (as measures of variability) or number (%).
- Comparison between categorical data was performed using Chi square test.
- Standard diagnostic indices including sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and diagnostic efficacy were calculated.
- \( p \)-value ≤0.05 was considered significant and <0.01 was considered highly significant.

Results

Among 50 patients included in this study, the mean age was 55 years (range 24-73 years). The most common complaint was post-menopausal bleeding (57.4%). The most common histological subtype was the endometrioid type detected in 84% of the patients with grade II being the commonest grade (53.7%). More than half of the included cases showed early presentation (n=14) and showed stage I endometrial carcinoma, 9 out of them were stage IA and 5 out of them were stage IB.

Overall staging with regards to the individual assessment of pre-contrast sequences that include T2WIs and DW-MRI and the DCE-MRI was done and correlated with the final operative staging, DWI was the most accurate as emphasized in (Table 2).

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Underestimation</th>
<th>Overestimation</th>
<th>Correct staging</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2WIs</td>
<td>0</td>
<td>5</td>
<td>20</td>
<td>80%</td>
</tr>
<tr>
<td>DW-MRI</td>
<td>0</td>
<td>3</td>
<td>22</td>
<td>88%</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>2</td>
<td>2</td>
<td>20</td>
<td>83.3%</td>
</tr>
</tbody>
</table>

Deep myometrial invasion was proved in 15 cases (60%) as reported by the surgical pathology, it was suggested by T2WIs in 18 cases (72 %) with overestimation of 3 cases, in 16 cases (64%) by DWI and DCE-MRI with overestimation of only 1 case.

Upon correlating the detection of deep myometrial invasion by T2WIs, DW-MRI and DCE-MRI with the final surgical pathology, DWI was the most accurate sequence (n=24/25, 96%) as shown in Table (3) and Fig. (1).

Cervical stromal invasion was reported in 7 cases by the final surgical pathology, it was suggested by T2WIs, DWI and DCE-MRI in 8 cases with overestimation of only 1 case. They all perform equally with a diagnostic accuracy, sensitivity, specificity, PPV and NPV of 96%, 100%, 94.4%, 87.5% and 100% respectively.

Diagnostic capability of T2WIs, DWI as well as DCE-MR images in detection of locally advanced and advanced malignancy was studied and positive features was detected in 4 cases. DW-MRI was the most sensitive and specific.

Detection of metastatic lymph nodes were proved in 4 cases as reported by the final surgical pathological results. T2WIs and DWI show equal sensitivity (75%), yet with specificity 78.1% and 81.3% respectively.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Efficacy</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2WIs</td>
<td>100%</td>
<td>70%</td>
<td>83.3%</td>
<td>100%</td>
<td>88%</td>
<td>0.001</td>
</tr>
<tr>
<td>DWI</td>
<td>100%</td>
<td>90%</td>
<td>93.8%</td>
<td>100%</td>
<td>96%</td>
<td>0.001</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>93.3%</td>
<td>90%</td>
<td>93.8%</td>
<td>88.9%</td>
<td>91.7%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table (2): Staging accuracy in 25 cases of endometrial carcinoma.

Table (3): Diagnostic indices of the ability to assess deep myometrial invasion in the studied group.
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Discussion

Pre-operative staging of endometrial carcinoma and evaluation of different prognostic factors is a challenge and is crucial for tailoring surgical approach and adjuvant treatment planning. Functional MR Imaging (fMRI) including DCE-MRI and DW-MRI are becoming part of the standard imaging protocols for staging [9].

The aim of our study is to depict the role of DW-MRI in comparison with DCE-MRI as a pre-operative tool for staging of endometrial carcinoma especially if contrast injection is contraindicated or not affordable.

In our study we had performed an individual assessment for T2WI sequence, the DW-MRI (fused with T2WIs) and DCE-MRI and we had evaluated the diagnostic performance of each of them with an achieved accuracy of 74% for conventional imaging, 88% for DW-MRI and 84% for DCE-MRI.

Over-and understaging:

In our study, results were similar to those performed by Beddy et al., [10] with more accurate overall staging of DW-MRI (88%) in comparison with T2WIs (80%) and DCE-MRI (83.3%). There is a tendency for overstaging with T2WIs (5 cases) and DWI (3 cases), yet there was no understaged cases. On the other side, with DCE-MRI, there were reported equal number of under-and overstaged cases (2 understaged and 2 overstaged).

The overstaging associated with DW-MRI interpretation was mostly attributed to lymph node detection (2 cases) and the unreliable criteria in differentiating reactive from metastatic lymph nodes. The third case was due to inaccurate myometrial invasion assessment.

Two cases were overstaged by T2WIs because of its reported pitfalls in myometrial invasion assessment (will be discussed later), two cases were attributed to lymph node detection and the last one due to false impression of bladder invasion.
In DCE-MRI, two cases were underestimated due to its limitation in advanced staging assessment (peritoneal thickening and deposits), one case related to lymph node detection and the last one due to inaccurate myometrial invasion assessment.

**Myometrial invasion:**

Accurate determination of the depth of myometrial invasion allows selection of patients for pelvic or para-aortic lymph node sampling whilst obviating the need for surgery in patients with low risk disease [2].

Although the majority of the published studies demonstrate that the addition of multiphase DCE-MRI to T2W imaging leads to a significant improvement in the accuracy of assessment of the deep myometrial invasion, some authors have found no significant difference.

Rockall et al., found that dynamic enhancement did not improve diagnostic performance in 84 patients when viewed independently of the T2W images [11]. Similarly Chung et al., found that administration of gadolinium did not distinguish myometrial invasion of tumor from normal myometrium in a subset of 24 patients in their study [12].

In the study performed by Beddy et al., the depth of myometrial invasion was assessed better by DWI [10]. In a prospective study published in European Radiology in 2010, Rechichi et al., found that DW-MRI was very accurate in assessing myometrial invasion they suggested that DWI could potentially replace dynamic imaging as an adjunct to routine T2WI for preoperative evaluation of endometrial cancer [13].

Moreover, Lin et al., stated that fused T2WI and DWI sequences could improve assessment of myometrial invasion. They found that the addition of fused T2/DWI sequences to standard T2WI and DCE-MRI improved pathological correlation significantly and was significantly more accurate than T2WI with DCE-MRI [8].

Shen et al., compared the use of DWI and DCE-MRI in the evaluation of depth of myometrial invasion and found that the diagnostic accuracy was 62% for DWI compared to 71% for DCE-MRI [14].

In our study, DW-MRI performed better than conventional T2WIs and DCE-MRI in the detection of deep myometrial invasion with a diagnostic accuracy reaching 96% versus 91.7% and 88% for DCE-MRI and T2WIs respectively. In T2WIs, deep myometrial invasion was suggested in 18 cases, 3 out of them were false positive (2 due to loss of junctional zone definition and the third one was due to confounding fibroid). In DWIs, deep invasion was considered in 16 cases, one of them was false positive (due to confounding interstitial fibroid). In DCE-MRI, deep myometrial invasion was considered in 16 cases, 1 false positive (probably due to extension of the tumor into the cornu); shown in Fig. (1) and 1 false negative (no deep invasion was evident; however heterogenous myometrial enhancement was noted).

**Cervical stromal invasion:**

The reported overall accuracy of MR imaging in detection of cervical stroma invasion is 90%-92%, with sensitivity of 91% and specificity of 96%. DCE-MRI (with a 180-240s delay) further enhances the detection of such invasion. Studies have demonstrated accuracy up to 98% (range 46%-98%), sensitivity up to 100% (range 33%-100%), and specificity up to 100% (range 87%-100%) [15].

In a study performed by Helal et al., in 2011, the overall MR imaging sensitivity, specificity and diagnostic accuracy were 64%, 66% and 65% respectively [16].

There is very little literature on the usefulness of DWI in detecting cervical stromal invasion in endometrial cancer. In the study performed by Beddy et al., in 2012, cervical stromal invasion was identified more often on the DWI than the DCE-MR images, however numbers are too small to draw any conclusions [10].

In our study, cervical stromal infiltration was detected in 8 cases out of 25 by T2WIs, DWIs and DCE-MRI with only 1 false positive case which is probably due technical error (inaccurate axial oblique scan plane). They all perform equally with a diagnostic accuracy, sensitivity, specificity, PPV and NPV of 96%, 100%, 94.4%, 87.5% and 100%.

**Locally advanced and advanced staging:**

To our knowledge; no previous scientific work had discussed the usefulness of DWI compared to DCE-MRI in the assessment of locally advanced and advanced stages of cervical carcinoma.

In our study; 4 cases were truly locally advanced and advanced stages. We had spotted variant signs of advanced malignancy which were: Peritoneal thickening and deposits, Peritoneal deposits with omental cake and enlarged paraaortic lymph nodes and Paraurethral metastatic deposits.
The overall accuracy of locally advanced and advanced stage assessment was 100% on DW-MRI versus 89.2% and 92.6% on T2WIs and DCE-MRI respectively. In our experience, DCE-MR had a limited ability in detection of peritoneal deposits. On the other side, DW imaging was very valuable in detection of drop metastases in the cervix or metastatic foci outside the uterus, such as adnexa, peritoneum and bone deposits. This is mostly achieved with high \( p \)-value where metastatic foci show diffusion restriction against a suppressed background.

Fuji et al., performed a study on 26 patients trying to evaluate the utility of DW-MRI for the detection of peritoneal dissemination in gynecologic malignancies, they showed that DWI was highly sensitive (90%) and specific (95.5%) for the evaluation of peritoneal dissemination [17].

Lymph node involvement:

Although systemic lymphadenectomy is part of the FIGO staging system of endometrial carcinoma, it carries significant risk of complications. Identification of the presence of nodal metastases would allow better selection of patients for lymphadenectomy and potentially avoid unnecessarily aggressive surgery [17].

Kim et al., [18] found that malignant nodes showed significantly less ADC values than those elicited by non-malignant nodes in patients undergoing lymph node dissection for cervical cancer. The sensitivity and specificity of ADC for differentiating metastatic from non-metastatic lymph nodes were 87% and 80%, respectively.

Nakai et al., evaluated nodal status at 1.5 T. In this study, the number of detected nodes improved, but they were not able to distinguish benign from malignant nodes using ADC values [19].

In our study, positive lymph node for metastasis was suggested by MR imaging in 11 cases by T2WI, in 5 cases by DCE-MR and in 7 cases by DWI. Following dissection metastatic nodes were proved in 4 cases with an overestimation analysis elicited by the pre-contrast (T2WI) and DWI and underestimation by the DCE-MRI. We measured ADC values for pathologically enlarged nodes. Values ranged between 0.85 \( \times 10^{-3} \) mm\(^2\)/s and 0.65 \( \times 10^{-3} \) mm\(^2\)/s for reactionary nodes and 0.74 \( \times 10^{-3} \) mm\(^2\)/s and 0.5 \( \times 10^{-3} \) mm\(^2\)/s for malignant nodes.

Our results were similar to Nakai et al., [19] concerning the superior ability of DW-MRI in detection of lymph nodes but it couldn't distinguish reactive from malignant lymph nodes. Accordingly, we found no relation between the absolute ADC values and the presence of metastatic deposits. However the ADC value was able to exclude lymph node metastasis in one case (1.2 \( \times 10^{-3} \) mm\(^2\)/s) with enlarged pelvic lymph node which was believed to be likely metastatic in view of its large size.

By measuring primary tumor ADC, lymph node ADC and lymph node long and short axis diameter, Lin et al., were able to increase their sensitivity for the detection of metastatic lymph nodes from 25% to 83% [20].

**Conclusion:**

DW-MRI was more accurate in assessment of deep myometrial invasion and was a very sensitive and specific tool in assessing locally advanced and advanced disease. DW-MRI and DCE-MRI were equally accurate is assessing cervical stromal invasion, yet DCE-MRI was very limited in proper detection of assessment of peritoneal deposits and distant metastatic spread.

**References**