Dynamic Contrast Enhanced MRI in the Staging of Cervical Carcinoma, Necessity or Luxury?

SHERIHAN F. DAKHLY, M.Sc.; WALID M. EL-KHAYAT, M.D. and DORRIA S. SALEM, M.D.
The Departments of Radiodiagnosis and Gynecology & Obstetrics, Faculty of Medicine, Cairo University

Abstract

Objective: To assess the value of Dynamic Contrast Enhanced MRI (DCE-MRI) versus conventional MR imaging and Diffusion Weighted Imaging (DWI) in the staging of cervical malignancies.

Methodology: Fifty cases of proved cancer cervix prior staging subjected to dynamic post contrast technique: One pre-and four post contrast phases. DWI was scanned using different p-values and ADC values were measured.

Results: DWI was the most accurate in staging operable cases (91%) and is the modality of choice for assessment of locally advanced carcinomas. Regarding detection of parametrial infiltration, DCE-MRI was less specific than DWI (86.6% versus 91.9%) yet more specific than T2WIs (88.6% versus 86.5%). In metastatic lymph nodes, DCE-MR showed the least accuracy of 86%.

Conclusion: DCE-MR can delineate local tumors and exclude bladder/rectal invasion. DWI is helpful in evaluate the local and distant extent of cervical malignancies.

Key Words: Cervical carcinoma – Dynamic contrast-enhanced MRI – Diffusion weighted MRI – Functional imaging.

Introduction

MANAGEMENT strategies of cervical cancer are either radical surgery in early-stage or primary chemo-and radiation therapy for patients with bulky tumors or locally advanced disease (stage IIB or greater) [1]. Thus staging of cervical cancer is crucial for planning the surgical approach and adjuvant treatment.

There are several limitations regarding the clinical staging of cervical cancer related to accurate estimation of the tumor size, parametrial and pelvic side wall invasion, and evaluation of nodal metastasis [2]. Accordingly, incorporation of cross sectional imaging (CT and MRI) was advised by the revised FIGO staging where available [3].

In conventional MR imaging, overestimation of parametrical infiltration as well as bladder and rectal invasion has urged the need for modifying the standard imaging protocol used in cervical cancer staging with incorporation of functional MR Imaging (fMRI) by means of Dynamic Multiphase Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) and Diffusion Weighted Magnetic Resonance Imaging (DW-MRI).

The purpose of that study is to depict the role of DCE-MRI, as a complementary tool to conventional MR imaging, in staging of cervical carcinoma in comparison with DW-MRI and if it is necessary to be incorporated in the standard imaging protocol putting in consideration its limitations; if contrast injection is contraindicated or not affordable.

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 cervical carcinoma after initial biopsy confirmation for pre-management staging to the Radiology Department in the period from February 2012 to April 2015.

They presented with pre-menopausal abnormal vaginal bleeding, postmenopausal bleeding and/or vaginal discharge. Prior staging using imaging...
was done; all cases were subjected to the following protocol:

1- Full history taking with a special emphasis on:
   Age, parity, history of replacement hormonal therapy or contraceptive therapy, previous gynecological problem or previous curettage, history of systemic disease or anticoagulant therapy.

2- Routine laboratory investigation for all patients including complete blood picture, random blood sugar, liver and kidney functions.

Magnetic Resonance (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 cervical cancer is explained in (Table 1).

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Plan</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>• T1 weighted.</td>
<td>Axial.</td>
<td>Evaluate bone marrow and lymph nodes.</td>
</tr>
<tr>
<td>• T2-weighted.</td>
<td>Axial oblique (perpendicular to the cervix), sagittal and coronal.</td>
<td>Visualize the tumor.</td>
</tr>
<tr>
<td>• DW-MRI.</td>
<td>Axial oblique.</td>
<td>Tumor characterization and its local extent.</td>
</tr>
<tr>
<td>• DCE-MRI (T1 THRIVE; high resolution isotropic volume examination).</td>
<td>Axial oblique at 0, 40, 60, and 120 and 240sec.</td>
<td>Visualize the tumor and its local extent.</td>
</tr>
<tr>
<td>• Fusion T2/DWI</td>
<td></td>
<td>Lymph node detection.</td>
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</table>

**Image analysis:**

I- MR image interpretation was performed by two consultants of radiology who were blinded about each other imaging findings and they were not aware about the tumor staging on pelvic US data reported at the time of initial evaluation. They were also blinded to the post-operative histopathological reports or the initial pre-therapy staging by Examination Under Anesthesia (EUA).

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

A- Tumor signal intensity on T1-,T2-weighted images and DW MR images.

B- Tumor size on T2-weighted images.

C- ADC measurement of the tumor and the suspected enlarged lymph nodes on ADC map.

D- Fusion images were primarily used to confirm or exclude the presence of parametrical infiltration, proximal isthmic extension, extent of vaginal invasion as well as pelvic organ invasion.

F- 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).

G- Metastatic disease.

Accordingly overall stage is given based on the revised FIGO staging system and was correlated with final pathological stage. In advanced cases of cervical cancer, results are correlated with methods approved by FIGO clinical staging.

**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.
• Comparison between mean values of ADC in the studied groups was performed using unpaired *t*-test.
• *p*-value < 0.05 was considered significant and <0.01 was considered highly significant.

**Results**

Fifty patients with pathologically proven cervical carcinoma with their age ranged between 30 to 80 years (mean 49 years) were included in our study. The commonest pathology of the included cases was squamous cell carcinoma (72%).

The stages of the included cases were: Stage IB (n=22, 44%), stage IIA (n=8, 16%), stage IIB (n=8, 16%), stage IIIB (n=10, 20%), stage IVA (n=1, 2%) and stage IVB (n=1, 2%).

The staging accuracy in 25 operable cases (stages IB-IIA) of cervical carcinoma is shown in (Table 2). DWI showed the most accurate assessment with an estimated value of 93.3%.

Parametrial infiltration was noted in 13 cases (26%); there was overestimation of 5 cases by T2WIs, 3 cases by DWI and 4 cases by DCE-MRI. Upon correlating the detection of parametrial invasion by T2WIs, DW-MRI and DCE-MRI with the final surgical pathology if available or examination under anesthesia, they perform equally regarding the sensitivity and negative predictive value. DCE-MRI was less specific than DWI (88.6% versus 91.9%) yet more specific than T2WIs (88.6% versus 86.5) as shown in (Table 3) and Fig. (1).

Proper detection of locally advanced and advanced stage is crucial for optimum adjuvant treatment planning in cervical carcinoma. 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 6 cases. Upon correlating the detection of locally advanced and advanced stages by T2WIs, DW-MRI and DCE-MRI with examination under anesthesia, resultant statistical indices were as shown in (Table 4).

Detection of metastatic lymph nodes is an important prognostic factor though not included in the FIGO clinical staging. The lymph node status was studied in the fifty patients to emphasize the role of T2WIs, DWIs and DCE-MR images in their characterization. Suspected MR findings were detected in 15 cases and findings were compared with the final surgical pathological results, DCE-MRI was the least sensitive (33.3%).

Proper LN assessment was limited by non-resection of lymph nodes in 14 cases despite morphological MR features of positive LN involvement as noted in 5 cases out of them. We measured ADC values for enlarged nodes. Values ranged between 0.85 X $10^{-3}$ mm^2/s and 0.65 X $10^{-3}$ mm^2/s for reactive nodes and 0.74 X $10^{-3}$ mm^2/s and 0.5 X $10^{-3}$ mm^2/s for malignant nodes.

The overall accuracy of T2WIs, DW-MRI and DCE-MRI in staging the 50 studied cases regarding the surgical staging/examination under anesthesia was 74% by T2WIs, 88% by DW-MRI and 83.3% by DCE-MRI.

### Table (2): Staging accuracy in 30 operable cases of cervical carcinoma.

<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>2</td>
<td>5</td>
<td>18</td>
<td>66.6%</td>
</tr>
<tr>
<td>DW-MRI</td>
<td>0</td>
<td>2</td>
<td>23</td>
<td>91%</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>2</td>
<td>2</td>
<td>20</td>
<td>83.3%</td>
</tr>
</tbody>
</table>

### Table (3): Diagnostic indices of the ability to assess parametrial infiltration in the studied group.

<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>86.5%</td>
<td>72.2%</td>
<td>100%</td>
<td>90%</td>
<td>0.001</td>
</tr>
<tr>
<td>DWI</td>
<td>100%</td>
<td>91.9%</td>
<td>81.3%</td>
<td>100%</td>
<td>94%</td>
<td>0.001</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>100%</td>
<td>88.6%</td>
<td>76.5%</td>
<td>100%</td>
<td>91.7%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table (4): Diagnostic indices of the ability to assess locally advanced and advanced stages in the studied group.

<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>80%</td>
<td>91.3%</td>
<td>80%</td>
<td>95.4%</td>
<td>89.2%</td>
<td>0.001</td>
</tr>
<tr>
<td>DWI</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0.001</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
<td>91.3%</td>
<td>92.6%</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Discussion

In our study we had performed an individual assessment for each of the pre-contrast sequence presented by the T2WI sequence, the DW-MRI (fused with T2WIs) and DCE-MRI and evaluated the diagnostic performance of each of them with an achieved accuracy of 66% for conventional imaging, 92% for DW-MRI and 83.3% for DCE-MRI.

Fifty female patients diagnosed pathologically with cervical carcinoma were included in that study. The majority were squamous cell carcinoma constituting 72%. 22 cases were stage IB, 8 cases were stage IIA, 8 cases were stage IIB, 10 cases were stage IIIB, 1 case was stage IVA and 1 case was stage IVB.

No papers discussing the usefulness of DWI compared with DCE-MRI in the overall staging and detection of parametrial infiltration in cervical cancer. We tried in this study to emphasize the role of DCE-MRI as a part of a standard imaging protocol in pre-treatment evaluation of cervical cancer and if it can be replaced by DWI and fused T2/DWIs.

Overall staging:

In our study, DW-MRI (with fusion images) performed better than T2WIs and DCE-MRI with
an overall accuracy of 92% by DW-MRI compared to 83.6% and 66.6% by DCE-MRI and T2WIs respectively. Overstaging with DW-MRI was noted in only two cases with no understaged cases, one was due to false detection of parametrial infiltration and the other one was due to false impression of lower third vaginal extension. This may be attributed to the reported pitfall of DW-MRI of restricted diffusion in highly cellular benign conditions.

Our results differ from what reported by Sala et al., who mentioned that contrast enhanced MR sequence is not needed for the staging of cervical cancer with no improvement in the overall staging compared to T2WI alone [4].

In our study, DCE-MRI helped much in achieving the proper staging: It excluded bowel infiltration, parametrial invasion and lower third vaginal infiltration when the reverse was suggested by T2WIs.

**Early tumor detection:**

Charles-Edwards et al., reported that DWI with an endovaginal interventional technique had improved tumor detection in stage Ia and Ib1 disease [5].

In our study, early tumor detection was achieved by DW MRI in one case appearing as a small focus of restricted diffusion with the estimated corresponding ADC measurement of $0.7 \times 10^{-3}$ mm/sec. That wasn’t possible in T2WIs that shows no definite mass, only abnormal signal related to post-biopsy changes.

**Parametrial infiltration:**

In our study overestimated parametrial invasion on T2WIs was noted in 5 cases. DWI-MRI and DCE-MRI had also overestimated 3 and 4 cases out of these 5 cases respectively. Parametrial invasion could be truly excluded on DW-MRI in 2 cases and on DCE-MRI in 1 case.

DW-MRI was more specific than T2WIs and DCE-MRI reaching up to 91.9% with estimated PPV of 81.3%. The three sequences are highly sensitive with a high negative predictive value reaching up to 100%.

**Advanced staging:**

In our study; 6 cases were considered truly locally advanced and advanced stages evidenced by: (1) Pelvic side wall invasion, (2) Lower third vaginal invasion, (3) Bowel infiltration, (4) Bone 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. Though DCE-MRI was the least sensitive (50%) with the least negative predictive value (91.3%), it was very valuable in exclusion of suspected bowel infiltration noted on T2WIs in one case and in raising our confidence to exclude bladder infiltration in another case. Yet it had a limited ability in detection of peritoneal and bone deposits, though retrograde we were able to detect them by the aid of DCE-MRI.

DW imaging is very valuable in detection of metastatic foci outside the uterus, such as adnexa, peritoneum and bone deposits. This is mostly achieved with high b-value where metastatic foci show diffusion restriction against a suppressed background.

A potential pitfall in interpretation of DW-MRI is water restriction in non-malignant tissues and benign condition. That was noted in 2 cases with ovarian hemorrhagic cysts with restricted diffusion. For this, images should always be evaluated together with ADC maps and other anatomical sequences (e.g. T1W and T2W images) in order to overcome such potential pitfalls in image interpretation.

**Lymph node involvement:**

Though not included in the FIGO clinical staging of cervical cancer, yet it is considered the most important prognostic factor. Kim et al., [6] found that malignant nodes showed significantly less ADC values than those elicited by non-malignant nodes. Our results were similar to Nakai et al., concerning the superior ability of DW-MRI in detection of lymph nodes but couldn’t distinguish reactive from malignant lymph nodes [7].

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% [8].

We observed that the background suppression on the DWI enhanced the visualization of the diseased nodes and specification into benign or malignant nodes was more applicable by adding the measured ADC values to the final radiologic diagnosis.

**Conclusion:**

DCE-MRI is beneficial in early stage cervical cancer through exact delineation of tumors and exclusion of bladder/rectal invasion. In the era of
cost-efficient health care, the routine incorporation of DCE-MRI in the standard protocol of cervical cancer pre-treatment evaluation is luxurious especially in the presence of more attractive tool; fused T2/DWI, offering the potential advantages of reduced scanning time and obviation of the intravenous administration of gadolinium-based contrast medium.

References


