Value of diffusion-weighted MR imaging in assessing response of neoadjuvant chemo and radiation therapy in locally advanced rectal cancer

Rania A. Marouf a, Mary Y. Tadros a,*, Tarek Y. Ahmed b

a Radiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
b Surgery Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Received 15 October 2014; accepted 23 March 2015
Available online 21 April 2015

Abstract Background: Rectal cancer is one of the most common tumors in industrialized countries and one of the most common malignant tumors of the gastrointestinal tract. MR imaging has become the most accurate technique in local staging of rectal cancer; this is due to advances in terms of imaging equipment, coils, and sequences that have progressively improved the technique, with a parallel increase in accuracy.

Objective: To assess the role of magnetic resonance imaging with diffusion in staging of rectal carcinoma before and after chemo and radiation therapy in relation to histopathological findings.

Materials and methods: The studied group included 19 patients proved to be rectal carcinoma by colonoscopy between October 2011 and December 2013. All patients were evaluated with conventional MRI and diffusion weighted images. Our population which was staged as Tx N2 M0 and T3–T4 Nx M0 stage, underwent MR and diffusion weighted imaging (DWI) before neoadjuvant chemo and radiation therapy and later 6–8 wks. After the end of the treatment they performed again MR for the re-staging of disease. The sensitivity, specificity and diagnostic accuracy for both examinations were calculated. Our gold standard was the histopathology.

Results: For T stage conventional MRI showed 60% sensitivity and 33% specificity with overall diagnostic accuracy 46.5% which increased after adding DWI to 87% sensitivity and 80% specificity with an overall accuracy 83.5%. N stage prediction by conventional MRI was 74% sensitivity and 80% specificity with an overall accuracy 78%. This increased after adding DWI to 83% sensitivity and 83% specificity with an overall accuracy 83%. MRI with DWI showed diagnostic accuracy 94.7%, and without DWI the diagnostic accuracy was 84.2%.

Conclusion: The use of additional DWI yields better diagnostic accuracy than does use of conventional MR imaging alone in the evaluation of complete response to neoadjuvant chemo radiotherapy in patients with locally advanced rectal cancer.

© 2015 The Authors. The Egyptian Society of Radiology and Nuclear Medicine. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
1. Introduction

Magnetic resonance (MR) imaging is the most promising technique for the local staging of rectal cancer (1). Diffusion-weighted MRI (DW-MRI) is becoming increasingly important in the assessment of malignant tumors.

In patients with rectal cancer who have received concurrent chemotherapy and radiation therapy (CCRT) before surgery, conventional magnetic resonance (MR) imaging has low accuracy in prediction of the pathologic stage owing to over staging or under staging.

The factors related to this problem include fibrosis, desmoplastic reaction, edema, inflammation, and viable tumor nets at a fibrotic scar from a previous tumor (2).

The aim of this study was to assess the role of magnetic resonance with diffusion in diagnosis, staging of rectal carcinoma in relation to histopathological findings.

2. Materials and methods

2.1. Subjects

The study was done in Ain Shams University Hospital and specialized private center in Cairo during the period from October 2011 till December 2013. Nineteen patients proved to be rectal carcinoma by colonoscopy were included in this study. Our population was staged as Tx N2 M0 (Table 1) and T3–T4 Nx M0, which underwent preoperative MR with and without diffusion before neoadjuvant chemo and radiation therapy. After the end of the treatment by 6–8 wks, they performed again MR for the re-staging of disease.

2.2. Acquisition and processing of MRI with and without diffusion

The study was performed with a 1.5-T MR system (Achieva; Philips Medical Systems, Best, The Netherlands). The examination was performed with phased-array surface coils. The patient is positioned supine. In some cases we used intrarectal gel for expanding the rectum and better delineation of the tumor. In other patients rectal enema was performed and in the rest of patients neither was used due to patients refusal. The phased-array surface coil is placed on the pelvis.

2.2.1. Scanning protocol

Localizer images in three orthogonal planes were taken first, then Sagittal, T2-weighted, fast (turbo) spin-echo sequence from one pelvic sidewall to the other (Sequence parameters TR 3500 ms TE 120 FOV = AP 270 RL 158 mm, voxel size RL 1.2 mm AP1.5 slice thickness 6 mm slice orientation sagittal).

Axial sections of the whole pelvis with large field of view T1 weighted images and T2 weighted images (T2 weighted images sequence parameters: TR 5500 ms TE 115 FOV = AP 270 RL 350 mm, slice thickness 6 mm, transverse slice orientation; T1 weighted images sequence parameters: TR 550 ms TE 24 FOV = AP 270 RL 350 mm, voxel size RL 1.2 mm AP1.5, slice thickness 6 mm, transverse slice orientation).

Magnified views with T2-weighted high resolution thin-section axial oblique images through the rectal cancer and adjacent tissues. This sequence was performed perpendicular to the long axis of the rectum and at the level of the tumor (Sequence parameter: TR 3500 ms TE 120 FOV = 270 TO 320 mm, voxel size RL 1.2 mm AP1.5, NSA 2 slice thickness 3 mm, axial oblique slice orientation).

A high-spatial-resolution coronal oblique T2 weighted imaging for patients with low rectal cancers (Sequence parameters: TR 3500 ms TE 120 FOV = 270 TO 320 mm, voxel size RL 1.2 mm AP1.5 slice thickness 3 mm).

The diffusion weighted imaging “DWI”: Axial DWI with single shot echo planar imaging (EPI) was performed at b
values of 0, 500 and 1000 s/mm². Postcontrast sequences (axial oblique, coronal oblique, sagittal oblique all parallel to the direction of the rectum).

2.3. Image analysis

MRI with DWI was done before and after neoadjuvant therapy with interval 6–8 wks where we assess the signal intensity change in T2 weighted images and postcontrast images then we add diffusion weighted images to assess viable tumoral tissue qualitatively then quantitatively by measuring the attenuation diffusion coefficient (ADC) values and comparing it with the pretherapeutically study using 1.2 × 10⁻³ mm²/sec as cutoff value to differentiate viable tissue from fibrosis within the mass and the LNs then restaging again and correlation of the result with the histopathological result.

2.4. ADC calculation

The mean ADC of the rectal mass was calculated by positioning multiple regions of interest (ROIs) over the tumor in consecutive image sections and then the mean ADC was calculated. We calculated the ADC value for each lymph node (LN) by placing the region of interest “ROI” well in the confines of the LN.

2.5. Statistical analysis

Statistical analysis was done using MedCalc® version 12.5 (MedCalc® Software bvba, Ostend, Belgium) and DAG stat (Mackinon, 2000). The paired t test was used to compare paired numerical data. To determine the diagnostic value of conventional MRI with and without DWI, series of 2 × 2 contingency tables were constructed to contrast the study of interest to the histopathological result. The following measures were then calculated: sensitivity, specificity, and overall diagnostic accuracy.

3. Results

Our study included 19 patients proved to be rectal carcinoma by colonoscopy ranging in age from 25 to 84 years old with the mean age 51.7 (11 males, 8 females). These cases presented primarily with bleeding per rectum. Our patients included 5 patients staged according to MRI as T4 and 14 staged as T3. These patients received adjuvant therapy for 6–8 weeks then restaging MRI was done. Using conventional MRI without DWI there was complete response in one patient, 10 staged as T2 and 8 staged as T3. When correlated with histopathological results the patient staged by MRI as T0 (complete response) was accurately staged, and 3 patients were accurately staged as T2 and 6 patients were accurately staged as T3.

This gives only one true negative and 9 true positive results giving 60% sensitivity and 33% specificity with an overall diagnostic accuracy 46.5%.

After adding DWI there was complete response in 4 patients (Fig. 1), 7 staged as T2 (Figs. 2 and 3) and 8 staged as T3. When correlated with histopathological results, 4 patients staged as T0 (complete response) were accurately staged, and 4 patients were accurately staged as T2 and 7 patients were accurately staged as T3 (see Tables 2–5). Table 2 shows correlation of the T stage after the adjuvant therapy with the pathological results using conventional MRI without DWI.

This gives 4 true negative and 11 true positive results giving 79% sensitivity and specificity 80% with an overall accuracy 79.5%. So the use of additional DWI yields better diagnostic accuracy than does use of conventional MR imaging alone in the evaluation of complete response to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer.

As regards the nodal staging after chemoradiotherapy, by conventional MRI without diffusion 32 LNs were detected, 13 suggested to be benign and 19 suggested to be malignant.

Among the 19 LNs suggested to be malignant by conventional MRI without diffusion, 2 LNs proved to be benign by histopathological evaluation (false positive), while among the 13 LNs diagnosed by MRI to be benign, 5 proved to be malignant by histopathological evaluation (false negative) with 6 LNs not detected at all by conventional MRI. This gives 74% sensitivity and 80% specificity with an overall accuracy 78%.

After adding the DWI and evaluation of ADC, 36 LNs were detected, 14 suggested to be benign and 22 suggested to be malignant.

Among the 22 LNs suggested to be malignant by DWI, 2 were proved to be benign by histopathological evaluation (false positive), while among the 14 LNs suggested to be benign by DWI, 4 LNs proved to be malignant by histopathological evaluation (false negative), with 2 LNs not detected at all by MRI with DWI. This gives 83% sensitivity and 83% specificity with an overall accuracy 83%.

There were no much increase in the diagnostic accuracy but there was increase in the detected LN as it highlights the LN but still there is difficulty in differentiating benign and malignant nodes.

4. Discussion

Rectal cancer is one of the most common tumors in industrialized countries and one of the most common malignant tumors of the gastrointestinal tract (3). During the past decade magnetic resonance imaging (MRI) has been proven to be the most accurate staging modality for primary rectal cancer (4). With preoperative imaging the T-stage, nodal involvement, and location of the tumor are evaluated, which determine the type of preoperative treatment. So far, MRI has not been able to accurately predict T-stage unless an endorectal coil is used (5). However, an endoluminal technique leads to less visibility of surrounding structures in the mesorectum because of the limited field of view. Endorectal MRI has good accuracy for identification of T1 tumors, and is therefore the examination of choice for staging superficial rectal cancer (6).

However, it is less accurate for staging of the more advanced tumors. Therefore MRI with phased-array coils is widely adopted as the most accurate technique for staging of these bulky T3 and T4 tumors (7).

DWI is becoming increasingly important in the assessment of malignant tumors. It is generally accepted that DWI enables noninvasive characterization of biologic tissues on the basis of their water diffusion properties (8). In our study we evaluate
Fig. 1a–d 1st pre adjuvant therapy conventional MRI: (a) axial oblique T2 FSE image shows uneven mural thickening at the upper rectum involving the mucosa and submucosa and focally invading the mesorectal fat. (b) Coronal oblique T2 FSE image shows the extent of rectal mass with no involvement of levator ms or anal sphincter complex. (c) Sagittal T2WI shows the distance to anal verge. (d) Axial oblique T1 postcontrast with fat suppression shows heterogeneously enhancing mass with left internal iliac LN with irregular border and heterogeneously enhancing as the rectal mass.

Fig. 1e–f Diffusion weighted imaging findings: (e) inversed diffusion weighted images, (f) the corresponding ADC map, both show that the mass and the regional LN show considerable degree of diffusion restriction on the corresponding area on the map giving low ADC values with mean ADC for the mass of $0.6 \times 10^{-3} \text{mm}^2/\text{sec}$, while for the left internal iliac LN of $0.7 \times 10^{-3} \text{mm}^2/\text{sec}$ keeping with malignant nature. Staging according to MRI criteria: The case was staged as T3bN1.

Fig. 1g–i 2nd stage MRI after adjuvant therapy: (g) axial oblique T2 FSE image, (h) T1-post-contrast fat suppression, and both show disappearance of the mural thickening. (i) Inversed diffusion weighted images at the level of previous rectal mass and LN show disappearance of the tiny perirectal LNs and left internal iliac LN. Restaging according to MRI criteria: Restaging after adjuvant therapy is suggested to be T0N0. Pathologically proved that there is good response with T0N1 stage (this is due to microscopic infiltration for tiny perirectal LN).
the role of MRI with diffusion in restaging of locally advanced rectal tumors as regards evaluation of the tumor response to chemoradiotherapy (CRT) and nodal restaging. Locally advanced rectal cancer has a poor prognosis because of the high frequency of metastasis and local recurrence. Concurrent chemoradiotherapy (CCRT) is performed in rectal cancer patients in whom the circumferential resection margin (CRM) or anal sphincter is threatened or involved, as identified at preoperative high-resolution pelvic MR imaging (9). After CCRT, the tumor response is classified as complete response (no residual tumor), partial response (tumor volume decreased > 50% or down staging), or no response after postoperative pathologic analysis of the tumor specimens. In our study the restaging using DWI with the calculation of ADC values gives 87% sensitivity and specificity 80% with overall accuracy 83.5% while using conventional MRI without DWI gives 60% sensitivity and specificity 33% with overall accuracy 46.5%. Few prior MR imaging studies have been conducted to assess the effect of long-course neoadjuvant CRT on the morphologic features of primary rectal cancer depending only on the change in T2 signal intensity without adding Diffusion weighted images. Similar studies reported that in restaging of irradiated rectal cancer, MR imaging had an accuracy of 52% for T stage (10). Another studies reported similar rates of MR imaging accuracy for T stage after CRT was 47% (11). The majority of the inaccuracies in both series were in over staging disease. This gives similar result to our study when evaluating T stage depending on morphological features using T2 weighted images with the inaccuracy in the over staging at T2 stage due to inability to differentiate fibrosis from tiny residual tumors tissue within the desmoplastic reaction induced by neoadjuvant therapy and also in the inability to diagnose complete response from residual tumoral tissues. Although MRI is considered the most accurate tool for primary tumor staging in rectal cancer, yet, this modality has intrinsic limitations in the differentiation of residual viable tumor from surrounding fibrosis after neoadjuvant CRT of rectal cancer. The fibrous tissue present after treatment causes

**Fig. 2a–c** 1st pre adjuvant therapy conventional MRI: (a) axial oblique T2 FSE image shows localized mural thickening at the midrectum with perilesional lymph node. (b) Axial oblique T2 FSE image at different level shows right sided perilesional LN, (c) Axial oblique T1 postcontrast with fat suppression shows heterogeneously enhancing mass with perimural haziness despite distension of the rectum, right perirectal LN with irregular border and heterogeneously enhancing as the rectal mass.

**Fig. 2d–e** Diffusion weighted imaging findings: (d) inversed DW images at different levels. The mass and the perirectal LN, both images show considerable degree of diffusion restriction. (e) The corresponding ADC map giving low ADC value with the mean ADC for the mass of $1 \times 10^{-3}$ mm²/sec while the LNs ranging between 0.6 and $0.9 \times 10^{-3}$ mm²/sec keeping with malignant nature. Staging according to MRI criteria: The case is suggested to be staged as T3aN1.
Fig. 2f–i  2nd stage MRI after adjuvant therapy: (f) axial oblique T2 FSE image, (g) sagittal T1-post-contrast fat suppression, both show disappearance of the mass with hypo intense diffuse wall thickening with no residual mass. (h) Inversed diffusion weighted images at the level of previous rectal mass, (i) ADC at the same level, both show disappearance of the tiny perirectal LNs with thin rim of diffusion restriction within the mural confines with low ADC values denoting favorable response to therapy yet with residual tumoral tissue within the confines of the wall. Restaging according to MRI criteria: Restaging after adjuvant therapy was T2N0. Pathologically proved that there is good response with T2N0 stage (adding DWI differentiates residual tissue from post therapeutic fibrosis).

Fig. 3a–d  1st pre adjuvant therapy conventional MRI: (a and b) sagittal T2 FSE shows large fungating mass along the proximal 1/3 of the rectum and rectosigmoid junction, and this tumoral tissue shows focal external extramural extension, (b) the mass abuts the uterus superiorly. (c and d) Axial oblique T2 FSE images, (c) show left internal iliac LN with irregular border although not enlarged yet harbor the same signal as the rectal mass, (d) show also tiny suspicious presacral LN.
Fig. 3g–j 2nd stage MRI after adjuvant therapy: (g) sagittal T2 FSE, (h) axial oblique T2 FSE, both show that the mural thickening becomes diffuse with perirectal stranding. (i) Inversed diffusion WI, (j) corresponding ADC map both show only area of diffusion restriction which confines to the wall with reduction of its ADC to $1 \times 10^{-3}$ mm$^2$/sec, disappearance of the perirectal LN and left internal iliac LN. Restaging according to MRI criteria: Restaging after adjuvant therapy was suggested to be T2N0. This case pathologically proved to have partial response with pathological stage T3aN0 stage (under staging owing to difficulty in differentiation between the desmoplastic reaction and tumoral infiltration at stage T3a).

Fig. 3e–f Diffusion weighted imaging findings: (e) inversed DW images at different levels. The mass and the perirectal LN show considerable degree of diffusion restriction, (f) the corresponding ADC map giving low ADC value with mean ADC for the mass $1 \times 10^{-3}$ mm$^2$/sec while the LNs ranging between $0.9$ and $1 \times 10^{-3}$ mm$^2$/sec keeping with malignant nature. Staging according to MRI criteria: The case was suggested to be staged as T4aN1.
thickening of the rectal wall. Thus, MR imaging cannot readily
differentiate T0 or T1 stage tumors from T2 stage tumors
because it is not possible to visualize individual rectal wall
layer (12). DWI has been shown to have several potential bene-
fits for the assessment of tumor localization and staging (13).

The ADC values obtained from DWI measurements reflect
tumor cellularity and anti-tumor treatment decreases tumor
cellularity, so CRT should increase the ADC value. Increased ADC values have also been correlated with tumor
necrosis and reduced cell density (14), and most studies (15–
17) have found an increase in ADC after CRT. Kim et al.
(15) showed that neoadjuvant CRT caused a significant
increase in the ADC values of 76 rectal cancer patients and
Cai et al. (16) showed that the tumor ADC values changed
during the course of neoadjuvant chemo radiation as the
ADC value at the 2nd week of therapy was significantly corre-
lated with the tumor response. Our study showed similar
results to these studies as there is significant increase in the
ADC values before and after CRT with the mean ADC values
prior to treatment were 0.7 after treatments 1.5 using 1.2 as
cutoff values to discriminate residual tumor from fibrosis.
Only a few studies have been performed to evaluate the added
value of DWI in determining a complete response (CR) to
neooadjuvant CRT. However, several authors have advocated
the use of DWI as a tumor response monitoring tool. Also
Kim et al. (15) concluded that DWI can be used to distinguish
favorable responders from poor responders to neooadjuvant
CRT with the mean ADC of the CR group was significantly
higher than that of the non-CR group. They reported that add-
ing DWI to T2-weighted imaging gave diagnostic accuracy
range of 82–85% and was more helpful for detecting viable
tumors after neoadjuvant CRT than T2-weighted imaging alone (accuracy 70%) in patients with locally advanced rectal
cancer. Our study gave similar results as when adding DWI,
there was significant increase in the diagnostic accuracy espe-
cially the specificity giving also high negative predictive value
as we were able to differentiate between complete responder
and non-responder. Song et al. (13) evaluated the added value
diffusion-weighted imaging (DWI) in combination with T2
weighted imaging (T2WI) compared with T2WI alone or posi-
tron emission tomography (PET)/CT for detecting viable
tumor after neoadjuvant chemo radiation therapy (CRT) in
patients with locally advanced rectal cancer. Their results were
that in detecting viable tumors, DWI with T2WI improved
diagnostic accuracies (90%) over T2WI alone (76%). The
sensitivity of DWI with T2WI was significantly higher than
those of T2WI alone. Their results showed agreement with
our results regarding the increased overall accuracy using
DWI + T2WI although the relatively high value using T2
alone at the study of Song et al. could be attributed to the
higher field strength (3 tesla) with better spatial and temporal
resolution at T2WI. It is difficult to differentiate a metastatic
lymph node and irradiated lymph node change with post-
CCRT MR imaging by using morphologic criteria. In particu-
lar, a change in a lymph node with or without metastasis after
CCRT is assumed to be associated with metastasis, resulting in
lymph node over staging (15). It is known that irradiated
malignant nodes often become partly necrotic resulting in
higher ADCs (17). Also Lambregts et al. (17) found that the
main role of DWI for lymph node evaluation was that it
improved the number of detected nodes, because nodes were
more easily detected on DWI due to their high signal intensity
compared with the suppressed background signal of surround-
ing tissues; as lymph nodes have a high cellular density, they
generally show restricted diffusion and are easily detected on
DWI. Our study comes in agreement with their study as regards
the increased detection rate of the involved LN where
by conventional MRI only 19 LNs were detected after the add-
ing DWI 36 LNs were detected. In conclusion the diagnostic
accuracy in the evaluation of chemo radiotherapy and tumor
response in case of locally advanced rectal tumors significantly
increased when DWI was added to conventional MR imaging.
So DWI has a growing role in rectal cancer staging and eval-
uating the post chemo radiotherapy state.

### Table 2

<table>
<thead>
<tr>
<th>T stage by MRI without DWI after CRT</th>
<th>Pathological stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
</tr>
<tr>
<td>T0</td>
<td>1</td>
</tr>
<tr>
<td>T2</td>
<td>10</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
</tr>
<tr>
<td>Total (cases)</td>
<td>19</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>T stage by MRI with DWI after CRT</th>
<th>Pathological stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
</tr>
<tr>
<td>T0</td>
<td>4</td>
</tr>
<tr>
<td>T2</td>
<td>7</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
</tr>
<tr>
<td>Total (cases)</td>
<td>19</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>N stage by MRI without DWI</th>
<th>Pathological stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
</tr>
<tr>
<td>Benign LN</td>
<td>13</td>
</tr>
<tr>
<td>Malignant LN</td>
<td>19</td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>N stage by MRI with DWI</th>
<th>Pathological stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
</tr>
<tr>
<td>Benign LN</td>
<td>14</td>
</tr>
<tr>
<td>Malignant LN</td>
<td>22</td>
</tr>
</tbody>
</table>
Conflict of Interest

There is no conflict of interest to declare.

References