The Use of Apparent Diffusion Coefficient as a Potential Marker of Rectal Cancer Aggressiveness Compared to Contrast Enhanced MRI in Pre Operative Staging of Rectal Carcinoma

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Abstract

Colorectal cancer ranks third amongst the most frequently diagnosed tumors in the world, after lung cancer and breast cancer.

Objective: To assess the value of MRI and diffusion MRI in characterization of rectal cancer and to investigate the potential use of the quantified ADC values as imaging biomarker of tumor aggressiveness thus helping in the preoperative staging of rectal carcinoma.

Subjects and Methods: 32 patients with rectal cancer were included at this prospective research study at National cancer institute. (19 women, 13 men) from July 2012 to March 2014.

Institutional Ethical Committee approval was obtained. All patients gave written consents. All patients were imaged with pelvic MRI examination. A minimum of five pulse sequences (axial T2, T1, and diffusion Wis together with coronal T1 and post contrast dynamic 3D fat sat. T1 Wis gradient study) were performed in all patients. The preoperative radiological staging and post operative pathological results were correlated. Patients with mucinous appearing tumors on the primary staging MRI were excluded.

Results: There was a statistically significant correlation between mean ADCs and different tumor T stage. \((p<0.001)\) with lower ADC values with higher the T stages.

Conclusion: The key MR sequence for rectal cancer staging is the T2. The addition of IV gadolinium-enhanced sequence did not improve the diagnostic accuracy for prediction of tumor penetration through the rectal wall. ADC values of rectal cancers significantly correlate with prognostic factors including the MRF status and the T and nodal stages.

Key Words: Rectal cancer – High resolution magnetic resonance imaging – Apparent Diffusion Coefficient factor (ADC).

Introduction

COLORECTAL cancer is the third most common cancer worldwide. Around 30-40% of colorectal cancers are located in the rectum, accounting for 5% of malignant tumors, and ranking as the fifth most common cancer in adults [1].

The current trends in the management of rectal cancer point toward a more widespread acceptance of neoadjuvant combined modalities therapies. These create an increasing need for preoperative imaging methods to noninvasively select high risk patients who could benefit from the more aggressive multimodality treatment approaches [2].

The aggressiveness of rectal tumors is expressed by several factors, including T stage, N stage, involvement of the Mesorectal Fascia (MRF), differentiation grade of the tumor, and the presence of lymphangio-vascular invasion [3].

MRI is considered as the modality of choice for rectal cancer staging. The high soft tissue contrast of MRI accurately assesses the extramural tumor extension and relation to Mesorectal Fascia (MRF) and sphincter complex [4].

At present, the use of Diffusion-Weighted Imaging (DWI) incorporated into a standard MR protocol is gradually increasing because of its proven benefit not only for tumor detection/characterization but also for monitoring treatment response [5].

DWI has proven useful for the assessment of tumor cellularity in soft tissue tumors and may be used as a powerful non invasive tool to monitor changes in tumor cellularity [6].

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The role of DW imaging in differentiating malignant from benign soft tissue lesions is still evolving when carefully applied, however, this modality has proved helpful in a subset of tumor types [7].

Diffusion weighted imaging measures water diffusion characteristics, which are dependent on multiple factors such as cell density, vascularity, viscosity of extracellular fluid, and cell membrane integrity. By quantifying these properties and expressing them as an Apparent Diffusion Coefficient (ADC), DWI could potentially be used as an imaging biomarker to better select patients with poor prognosis who will truly benefit from a more aggressive neoadjuvant treatment [8].

The value of ADC as a quantitative biomarker in patients with rectal cancer is not clear yet. Data are scarce and most published data on the value of DW-MRI for prediction of response to chemoradiation are conflicting [9].

Material and Methods

32 patients with rectal cancer were included in this study (19 female and 13 male), age ranges from 21 to 82 years with the mean age 51 years. The cases were studied at national cancer institute from July 2012 to May 2014. The diagnosis of rectal carcinoma in these patients was established based on their symptomatology, clinical examination, proctoscopy and biopsy.

Inclusion criteria:
- Pathologically proven rectal carcinoma.
- Treatment plan by surgical resection with or without neoadjuvant therapy.
- Availability of pathological reports of surgical specimens mentioning tumor differentiation grade.
- Availability of primary staging MRI including DWI.

Exclusion criteria:
- Non neoplastic rectal masses.
- Patients with mucinous appearing tumors on the primary staging MRI (completely hyperintense on T2-weighted images without any solid tumor parts) were excluded, because they are known to have low cellular density, exhibiting high ADC values and as such potentially introducing a bias in the study results.

MRI technique:
All the patients were imaged on 1.5T MRI machine (1.5-T Philips, Achieva, Release 3.1) with pelvic array coil. The patients were asked to perform rectal wash 2 hours before the MRI examination using a rectal enema. The patient lies in the lateral decubitus at the MRI machine and Foley's catheter was inserted into the anal canal and luminal distention by warm gel (60-100ml) was done. The used sequence protocols for MR imaging of the rectum was standardized. The use of both T2 and T1, diffusion weighted sequences with acquisition of contrast enhanced sequences. At least five pulse sequences (axial T2, T1, and diffusion Wis together with coronal T 1 and post contrast dynamic fat sat. T1 weighted gradient study) were performed in all patients. High resolution T2 Wis. has been used in all cases, with images being obtained using a fast spin echo sequence. The sagittal images were used to plan the axial images as a localizer (the scan plane was perpendicular to the tumor bulk), and coronal images (scan plane angled parallel to the long axis of the rectum); TR/TE, 4000-5000/100; slice thickness 3mm; image gap 0; Echo train length 16; FOV 18-24; 256 X 256 matrix; No. of signal acquired 6; acquisition time 5-7min.

Axial diffusion sequence:
DW imaging was performed in the transverse plane with tri-directional diffusion gradients by using b values 0, 300 and 600sec/mm² to increase sensitivity to cellular packing. Repetition time (TR)=1.4sec, echo time (TE)=60msec, number of excitations (NEX)=3, matrix 256 X 256 with a field of view 270mm, slice thickness 3mm, slice gap 1-2mm, scan time 1.58min. To ensure that the same areas were measured, regions of interest were copied and pasted from DW images to ADC maps. Apparent diffusion coefficient maps in grayscale were automatically generated at the operating system, using a mono-exponential decay model including all three b-values.

ADC calculation:
Mean ADC was calculated from a sample of three round/oval-shaped Regions of Interest (ROIs) that were manually placed within solid tumor parts (as identified as focal masses showing intermediate signal intensity on the anatomical T2-weighted images) of three independent tumor-containing slices. The size and position of the ROIs was chosen to include as much of the solid tumor area as possible.

T staging interpretations:
- T1 was staged as if tumor confined to the mucosal layer of rectal wall.
- T2 was staged if there was invasion of the rectal layer up to the muscularis propria with no penetration of the muscularis propria or perirectal fat.
• T3 was staged if there was invasion of all rectal layers with perirectal fat infiltration yet without pelvic organ involvement.
• T4 was staged if there was invasion of mesorectal fascia and visceral peritoneum or surrounding organ infiltration.

**LNs staging interpretations:**
• N0 is diagnosed if there was no lymph nodes metastasis.
• N1 is diagnosed if there were metastasis in 1-3 lymph nodes.
• N2 is diagnosed if there were metastasis in 4 or more perirectal lymph nodes.

**Mesorectal fascia invasion interpretations:**

The mesorectal fascia encircles the rectum and the mesorectal fat, nodes, and lymphatic vessels to form a distinct Anatomic Unit. It is easily identified on axial T2-weighted images as a thin hypointense line. The mesorectal fascia invasion was defined as tumor signal intensity extends through it into adjacent structure or viscus.

**Circumferential Resection Margin (CRM) interpretations:**

CRM is the distance between the outer margin of tumor and the mesorectal fascia and is critical for surgical planning, potential recurrence after Total Mesorectal Excision (TME). An involved CRM was assumed if the shortest distance from either the extramural tumor extension, a suspected lymph node or a tumor deposit in the mesorectum, to the mesorectal fascia was <1 mm.

This crucial distance of at least 2mm can be predicted with 97% confidence when the distance between a tumor and the mesorectal fascia on MRI is at least 6mm.

**Statistical methods:**

Data were coded and entered using the statistical package SPSS version 23. Data was summarized using mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t-test when comparing 2 groups and analysis of variance (ANOVA) with multiple comparisons post hoc test when comparing more than 2 groups. For comparing categorical data, Chi square (χ²) test was performed. Exact test was used instead when the expected frequency is less than 5. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of ADC for detection of severity of tumors. *p*-values less than 0.05 were considered as statistically significant.

**Results**

**General criteria:**

This study included 32 patients, age ranges from 21 to 82 years with the mean age 51 years. Sex predilection is demonstrated in Fig. (1).

![Sex predilection in the study.](image)

The accuracy, sensitivity, specificity of T2-weighted MR images alone versus combined T2-weighted images plus gadolinium-enhanced T1 weighted MR images for the prediction of rectal wall penetration was assessed with accuracy 96.9%, sensitivity 92.9% and specificity 100% (Table 1). Out of 32 patients in this study, 2 patients were staged as T2 stage by both T2WI and contrast-enhanced T 1 WI, 12 patients were staged as T3 by T2WI but 11 patients were staged as T3 by contrast-enhanced T1WI and 18 patients were diagnosed as T4 by T2WI only while 19 patients were staged as T4 by contrast-enhanced T 1 WI creating (*p*-value =<0.001).

**Table (1): Contrast enhanced T1 -weighted MR sequences and rectal wall penetration.**

<table>
<thead>
<tr>
<th>T stage</th>
<th>Count</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>2</td>
<td>26.2</td>
</tr>
<tr>
<td>T3</td>
<td>11</td>
<td>34.4</td>
</tr>
<tr>
<td>T4</td>
<td>19</td>
<td>59.4</td>
</tr>
</tbody>
</table>

The accuracy, sensitivity, specificity of T2-weighted MR images vs contrast-enhanced T 1 MR images in tumor extension into mesorectal fascia (Table 2).

T2-weighted MR images vs contrast-enhanced T 1 MR images in tumor extension into mesorectal fascia (Table 2).

The accuracy, sensitivity, specificity of T2-weighted MR images alone versus combined T2-weighted images plus gadolinium-enhanced T1 weighted MR images for the prediction of tumor
The Use of ADC as a Potential Marker of Rectal Cancer Aggressiveness Compared

Extension into the mesorectal fascia was accuracy 100%, sensitivity 100% and specificity 100%. Out of 32 patients in this study, 20 patients were diagnosed with involved MRF by both T2WI and Contrast-enhanced T1 WI and 12 patients were diagnosed as MRF free by both T2WI and contrast enhanced T1WI creating (p-value=<0.001).

Table (2): Contrast enhanced T1-weighted MR and tumor extension into the Mesorectal Fascia.

<table>
<thead>
<tr>
<th>Tumor extension in the MRF:</th>
<th>Tumor</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>20</td>
<td>62.5</td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>37.5</td>
</tr>
</tbody>
</table>

The histopathological results in the 32 patients showed adenocarcinoma in all of them with moderate differentiation, Grade II.

The MRI based findings: 2 patients were staged as T2, 12 as T3 and the remaining 18 were considered to be T4, 4 patients were staged as N0 while 28 had positive nodal disease (N1 and N2). The MRF was free in 12 patients and involved by tumor in the remaining 20.

![Fig. (2): MRI and histopathological findings.](image)

Table (3): MRI and histopathological findings.

<table>
<thead>
<tr>
<th>Pathology:</th>
<th>Count</th>
<th>%</th>
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<tbody>
<tr>
<td>Adenocarcinoma, Grade 2</td>
<td>32</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRF invasion:</th>
<th>Count</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>20</td>
<td>62.5</td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>37.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymph nodes involvement:</th>
<th>Count</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>28</td>
<td>87.5</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>12.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T Stage:</th>
<th>Count</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>2</td>
<td>6.2</td>
</tr>
<tr>
<td>T3</td>
<td>12</td>
<td>37.5</td>
</tr>
<tr>
<td>T4</td>
<td>18</td>
<td>56.2</td>
</tr>
</tbody>
</table>

Correlation between ADC and prognostic factors:

The mean tumor ADC for the whole patient population was 0.981 ± 0.276 X 10^-3 mm^2/sec. The difference in ADC values between different groups and their associations with various radiological parameters are outlined in (Table 3).

Table (4): Correlation between ADC values and prognostic values.

<table>
<thead>
<tr>
<th>ADC value (mean ± SD) X 10^-3 mm^2/sec</th>
<th>p-value</th>
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<tbody>
<tr>
<td>MRF invasion:</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
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<td>No</td>
<td>12</td>
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<tr>
<td>Lymph nodes involvement:</td>
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<td>28</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
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<td>T2</td>
<td>2</td>
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<tr>
<td>T3</td>
<td>12</td>
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<tr>
<td>T4</td>
<td>18</td>
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</table>

Discussion

Colorectal cancer is the third cause of cancer worldwide; it accounts for a large number of tumor related deaths and recurrence occurs in about one-third of patients within the first 2 years after surgery [4].

MRI is currently the only imaging modality for preoperative staging of rectal carcinoma [8].

Regarding the use of contrast medium, injection of intravenous contrast (Gadolinium) does not add to the accuracy of staging.

Contrast enhanced T1-weighted MR sequences and rectal wall penetration:

The results of the present study show that the addition of gadolinium-enhanced T1-weighted MR sequences to T2-weighted fast SE MR sequences didn't significantly improve the diagnostic accuracy for the prediction of tumor penetration through the rectal wall as in all of the 32 patients, both T2WI and contrast-enhanced T1WI gave the same results about T stage except in one case where over staging has occurred in the contrast study creating an accuracy 96.9%, sensitivity 92.9% and specificity 100%. Thus the information given by contrast study was also obtained by T2WI, so contrast study didn’t add to the diagnostic accuracy of T2WI and therefore it can be omitted.
Contrast enhanced T1-weighted MR and tumor extension into mesorectal fascia:

Results of our study showed that the addition of gadolinium-enhanced T1-weighted MR imaging does not improve the high accuracy (approximately 90%) of T2-weighted fast SE MR imaging for the evaluation of tumor invasion in the mesorectal fascia as in all of the 32 patients, both T2WI and contrast-enhanced T1WI gave the same results about MRF status creating an accuracy 100%, sensitivity 100% and specificity 100%. Thus the information given by contrast study was also obtained by T2WI, so contrast study didn’t add to the diagnostic accuracy of T2WI and therefore it can be omitted thus saving acquisition time and examination costs and avoiding potential allergic reactions.

In a study of 43 patients with rectal cancer, Jhaveri et al. [4] found an accuracy, sensitivity, and specificity of 95%, 67%, and 100%, respectively, for prediction of the circumferential resection margin.

This study supported the idea that gadolinium based contrast material is not essential for the determination of tumor extension into the mesorectal fascia.

Regarding the value of DW-MRI as a potential noninvasive imaging marker of tumor aggressiveness in rectal cancer:

The aggressiveness of rectal tumors is expressed by several factors, including T stage, N stage, and involvement of the Mesorectal Fascia (MRF) which are traditionally assessed by histopathological examination of the surgical specimen.

The goal of the current work was to assess the value of DW-MRI as a potential noninvasive imaging marker of tumor aggressiveness in rectal cancer.

This study was conducted on 32 patients, according to the MRF status, 20 patients were diagnosed as MRF+ve by MRI with the mean ADC of 0.905 X 10^{-2} mm^2/sec while 12 patients were diagnosed as MRF-ve with the mean ADC of 1.109 X 10^{-2} mm^2/sec creating a statistically significant correlation between ADC and MRF status (p-value=0.04). According to T stage, 2 patients were diagnosed as stage T2 with the mean ADC value of 1.750 X 10^{-2} mm^2/sec, 12 patients were diagnosed as stage T3 with the mean ADC value of 0.971 X 10^{-2} mm^2/sec while 18 patients were diagnosed as stage T4, with the mean ADC value of 0.903 X 10^{-2} mm^2/sec creating a statistically significant correlation between ADC and T stage (p-value<0.001). According to the nodal status, 28 patients were diagnosed as LN+ve with the mean ADC value of 0.968 X 10^{-2} mm^2/sec and 4 patients were diagnosed as LN-ve with the mean ADC value of 1.074 X 10^{-2} mm^2/sec creating a non-statistically significant correlation between ADC and N stage (p-value=0.478).

In the current study pretreatment mean ADC was significantly lower for tumors invading MRF or tumors with higher T stage and tumors with positive nodal disease although the latter was not statistically significant. This is an interesting finding as it is proven that both MRF involvement and positive lymph nodes are powerful predictors of a local recurrence and distant metastases. Presence of any correlation between ADC and MRF or T stage or nodal status, therefore, suggests that ADC on itself correlates with prognosis. This could be explained by the fact that ADC values are indirectly derived from a tumor’s cellular microarchitecture and may thus reflect the aggressiveness of the tumor tissue profile.

The results in this study were comparable to many other studies:

The results of a study done by Curvo-Semedo et al., [2] on 50 patients, demonstrated that there was a statistically significant correlation between ADC value and clinical MRF status (p-value=0.013) and nodal status (p-value=0.011) on MR imaging and tumor differentiation grade upon histological examination (p-value=0.025) while there was no significant correlation between ADC and the T stage at primary MRI (p-value=0.064), however we didn’t include the histological differentiation grade in our study as all patients in the current study group were grade 2 (moderately differentiated) and that wouldn’t be representative of the value of tumor differentiation grade. The results of the current study agreed with him that we found significant correlation between the ADC value and the clinical MRF status (p-value=0.04) and we disagreed with him that in the current study, we found a significant correlation between ADC values and T stage (p-value<0.001) and there is no significant correlation between ADC values and nodal status at primary MRI (p-value=0.478).

In a study done by Oka et al., [6] on 40 patients, which showed significant correlation between ADC values and tumor differentiation grade (p=0.019) and there was no significant correlation between ADC and T stage (p=0.59) and the presence of MRF invasion (p=0.71) and N stage (p=0.41).
The results of the current study are consistent with their results about the nodal status that we found no significant correlation between ADC values and nodal stage at primary MRI ($p$-value= 0.478) and we were inconsistent with their results about the T stage and MRF status as the current results show significant correlation between the ADC value and the clinical MRF status ($p$-value =0.04) and T stage ($p$-value <0.001).

In our study ADC measurements were obtained by measuring three sample ROIs, which may not be fully representative for the overall tumor profile and this approach was chosen because outlining of the whole tumor volume is very time-consuming and difficult to perform in clinical practice.

**Conclusion:**

The most suitable MR sequence for rectal cancer staging is the T2 weighted image sequence as it best depicts the anatomy of the rectal wall.

The addition of IV gadolinium enhanced T 1 weighted sequence did not improve the diagnostic accuracy for prediction of tumor penetration through the rectal wall or tumor involvement of the mesorectal fascia.

ADC values of rectal cancers significantly correlate with prognostic factors including the MRF status and the T stage. There is a tendency toward lower ADC values in tumors with involvement of the MRF, node-positive tumors and higher T stage which are the cancers with poorer prognosis. Our study suggests that ADC has the potential to become an imaging biomarker of tumor biological profile.

**References**

الملخص العربي

المقدمة والهدف من الدراسة: يعد سرطان المستقيم هو ثاني أكثر أورام الجهاز الهضمي شيوعاً في العالم وعادة ما يؤدي الارتجاع المكى للورم بعد الاستئصال الجراحي إلى مرض عضلي. وتوقع كيفية تطور سرطان المستقيم تيتم على عدة عوامل، بعضها يتم تقديره تقليدياً عن طريق الفحص الميكروسكوبى للأنسجة بالعينة الجراحية وتتمثل في مسافة اختراق الورم لجدار المستقيم وعدد الغدد المقاومة للمصابة بورم وإصابة سرائقر المستقيم والتي يمكن تقديرها أيضاً بالرنين المغنطيسي قبل التدخل الجراحي.

واستهدف هذا الدراسة استعراض وقيمة استخدام معامل الانتشار الناهج ككلمة محتملة على عين سرطان المستقيم مقارنة بالرنين المغنطيسي التقليدي المعزز بالصيغة.

المتعرض وطريقة البحث: فانتى إجراء هذه الدراسة على 43 من مرضى سرطان المستقيم بمعهد الأورام القومي جامعة القاهرة وذلك في الفترة من يوليو 2012 وحتى مارس 2014 بعد إجازة لجهة أخلاقيات البحث العلمي بمعهد الأورام.

تم تصور كل المرضى بعد اخذ موافقة كتابية منهم وذلك بمعدل خمسة متابعة تصوير ويتضمن زمن تصوير أول وثاني في أوضاع مختلفة ويتم أضافة التصوير بالانتشار وما بعد الصبغة.

تم تقييم المرحلة الورمية بالأشعة في كل المرضى ومقارنتها بنتائج تحليل الأنسجة ما بعد الجراحة مع استعداد المرضى ب أصحاب الأورام الخبيثة الجيلابليتية.

النتائج: في دراستنا كانت هناك علاقة إيجابية ذات دلالة إحصائية بين متوسط معاملات الانتشار الموزون ومراحل تدرج الورم المختلفة.

ووجد إن معامل الانتشار تقل كمadapter مراحل تدرج الورم.

الخلاصة: وقد خلصت نتائج هذه الدراسة إلى أن معامل الانتشار الموزون يعطي قيمة أقل كمadapter مسافة اختراق الورم بعد جدار المستقيم. وكذلك زاد عدد الغدد المقاومة المصابة بالورم بعد إصابة سرائقر المستقيم وكمل هذه العوامل تدل على توقع أسوأ تطور الورم وبالتالي يمكن استخدام التصوير بالرنين الإشارة الموزون ومعامل الانتشار الموزون كعامل من أجل اختيار المرضى الذين سيستفيدون من علاج كيماوي أو أشعاعي وذلك للفحص التشخيص واختيار الطرق الأفضل للعلاج.

كما خلصت نتائج البحث إلى أن زمن التصوير الثاني في الرنين المغنطيسي يعطى نتائج دقيقة وأن استخدام الصبغة في فحص الرنين المغنطيسي لم يحسن الدقة التشخيصية في تشخيص مدى سماكة اختراق الورم بعد جدار المستقيم أو تشخيص إصابة سرائقر المستقيم

ولذلك يمكن عدم استخدام الصبغة في فحص الرنين المغنطيسي.