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DWI in Assessing Aggressiveness of Rectal Cancer

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ABSTRACT

Background: diffusion-weighted magnetic resonance imaging (DW-MRI) permits non-invasive assessment of tumor characteristics.

Aim of the work: this study was aimed to emphasize the role of DWI in assessing aggressiveness of rectal cancer with the histopathological correlation.

Patients and methods: this was a prospective study that included thirty patients with histopathological proved rectal carcinoma referred from the Surgical Department, Ain Shams University Hospitals to the MRI Radiology Unit for Rectal Cancer Staging.

Pelvic MRI study with conventional sequences and DWI were performed.

Results: 81% of moderately differentiated adenocarcinoma (ADC) (grade II) showed restricted diffusion with low signals in ADC sequence, while none of the poorly differentiated adenocarcinoma (grade III) showed restricted diffusion with high signals in ADC sequence (T2 shin-through). There was a high statistically significant difference in characterization of poorly (grade III) and moderately differentiated adenocarcinomas (grade II).

Conclusion: significant correlations were detected between mean ADC values and differentiation grade. ADC may be useful as an imaging tool for re-staging of tumor aggressiveness, but it cannot serve as an independent tool for primary staging of rectal cancer.

Keywords: magnetic resonance imaging, MRI, diffusion weighted imaging, DWI, rectal cancer, diagnosis, pathology staging and disease assessment

INTRODUCTION

Colorectal cancer is the second most common cancer in women and the third most common cancer in men. In recent years, mortality rates have decreased due to major changes in therapeutic management, in particular the standardization of the operative procedure and more important accurate pre-operative strategy depending on imaging [1].

Around 40–50% of colorectal cancers are located in the rectum. Rectal cancer is defined as a tumor whose margin measured with the rigid rectoscope was 16 cm or less from the cutaneous line [2]. Preoperative imaging for rectal cancer staging is also useful to determine which surgical technique would be more appropriate. Ideal imaging modality should accurately assess the depth of tumor penetration (T), lymph node involvement (N), presence of distant metastatic disease (M), mesorectal fascia involvement, and anal sphincter involvement which affect the prognosis of rectal cancer [3].

MRI is currently one of the most accurate noninvasive modalities for staging rectal carcinoma. The introduction of phased-array coil and the development of T2-weighted fast-spin sequences have enabled accurate determination of prognostic factors and anatomic assessment of the pelvis by delineating rectal tumors through increases in spatial and contrast resolution.MRI has overall accuracies for T staging of 65–86% [4].

Due to its ability to detect and characterize tumors diffusion weighted imaging (DWI) is increasingly incorporated into standard magnetic resonance imaging (MRI) protocols for tumor imaging [5].

Moreover, when the DWI is co-registered with T2W images, the T-staging can be performed with high accuracy [6].

The aim of the current work was to emphasize the role of DWI in assessing aggressiveness of rectal cancer with the histopathological correlation.

PATIENTS and METHODS

This prospective study was approved by an institutional review board; informed consent was obtained from all patients. The study population included 30 patients with rectal cancer referred from the Surgical Department, to the MRI Radiology Unit, Ain Shams University Hospitals, Cairo, Egypt, for Rectal Cancer Staging, during the period of Dec 2016 to Oct 2017.

Inclusion criteria were patients who had histopathologically proved rectal cancer and were

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not treated with pre-operative chemotherapy and/or radiotherapy.

Exclusion criteria were patients with non neoplastic rectal masses and patients known to have contraindications for MRI as: claustrophobia, pacemaker, cochlear implants, artificial joints, artificial heart valves, metal clips from aneurysm surgery and bullet or other metal fragments.

Data were statistically described in terms of mean, standard deviation (SD) and range, or frequencies (number of cases) and percentages when appropriate. Agreement between MRI and pathology was tested using kappa statistic. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Machine used: 1.5 Tesla Magnetic Resonance (Philips Achieva 16 channels) equipped with a phased-array surface coil.

MR IMAGING TECHNIQUE

Axial images obtained orthogonal to the tumor plane, with an in-plane resolution of 0.5–0.8 mm. **T2W TSE images in axial plane:** TR=3500msec, TE=80msec, matrix 204×125, FOV=250 mm, slice thickness=3 mm, slice gap=2mm, scan duration=1.17min and flip angle=90◦.

T2W TSE images in sagittal plane: TR=3500msec, TE=80msec, matrix 204×125, FOV=250 mm, slice thickness=3 mm, slice gap=2mm, scan duration=1.17min and flip angle=90◦.

T2W TSE images in coronal oblique plane: TR=3500msec, TE=80msec, matrix 320×256, FOV=250 mm, slice thickness=3 mm, slice gap=2mm, scan duration=1.17min and flip angle=90◦.

Diffusion weighted imaging: DW imaging was performed in the transverse plane with tri-directional diffusion gradients by using b values 0, 300 & 600 sec/mm2 to increase sensitivity to cellular packing. The other parameters were as follows: TR=1.4sec, TE=60msec, NEX=3, matrix 256×256, FOV=270mm, slice thickness=3mm, slice gap=1-2mm and scan time=1.58 min to ensure that the same areas were measured; regions of interest were copied and pasted from DW images to ADC maps.

ADC calculation: we calculated the ADC value from a sample of three round/oval-shaped regions of interest (ROIs) that were manually placed within solid tumor parts (It was identified as focal masses showing intermediate signal intensity on the anatomical T2W images) of one or two tumor-containing slices. The size and position of the ROIs were chosen to include as much of the solid tumor area as possible.

T1 Post contrast fat suppression in axial, sagittal, and coronal planes.

HISTOPATHOLOGIC EVALUATION

After surgery, the resected specimens were staged according to the International Union Against Cancer pTNM staging system [7].

Hematoxylin and eosin–stained slices were prepared and pathologists reviewed specimens for all patients. Proximal, distal, and circumferential resection margins were evaluated. A careful search of the mesorectum was performed to identify as many lymph nodes as possible

The study was approved by the Ethics Board of Ain Shams University.

RESULTS

Thirty patients were included in this study with mean age of 50 ±14.6 years. All patients had pathologically proven rectal carcinoma; 17 cases were diagnosed as moderately differentiated adenocarcinomas, 7 cases as well differentiated adenocarcinomas and 6 cases as poorly differentiated adenocarcinoma **(Fig. 1)**. The tumor was located in the lower 1/3 of the rectum (0-5 cm from the anal verge) in 19 cases, in the middle third (5-10 cm from the anal verge) in 8 cases and in the upper third (10-15 cm from the anal verge) in 3 cases **(Table 1)**. From this table we found that the tumor is located in lower third of rectum in 63.35 % of cases.

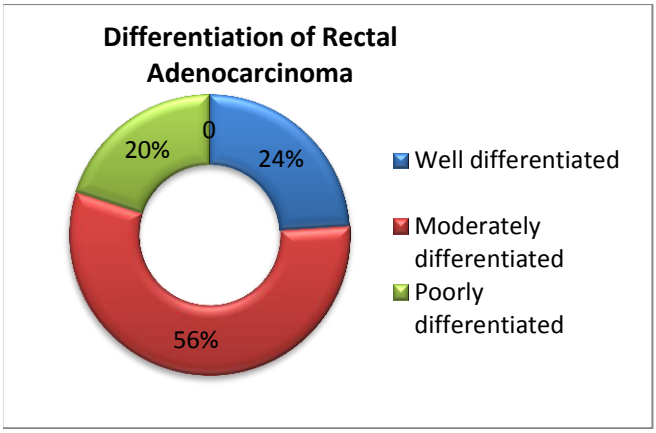

Figure 1: percentage of types of adenocarcinomas according to the histopathological classification.

Table 1: percentage of rectal cancer lesion's location

Position	Number	%
Lower rectal (0-5 cm from anal verge)	**19**	**63.35 %**
Mid rectal (5-10 cm from anal verge)	**8**	**26.65 %**
Upper rectal (10-15 cm from anal verge)	**3**	**10 %**

81% of moderately differentiated adenocarcinoma (grade II) showed restricted diffusion in terms if bright DWI signals in high b-value (600-800) with low signals in ADC sequence, while none of the poorly differentiated adenocarcinoma (grade III) showed restricted diffusion. The well differentiated adenocarcinoma showed restricted diffusion in 100% of cases **(Fig. 2)**.

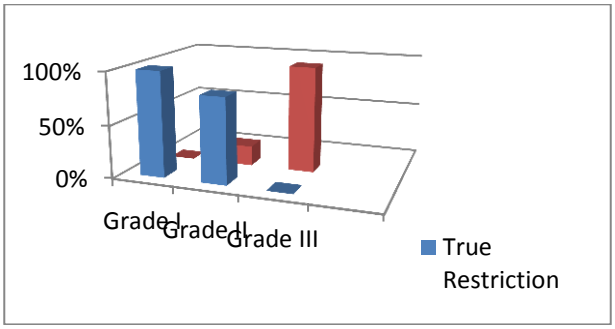

Figure 2: lesion characterization by diffusion restriction.

The diffusion restriction parameter in diffusion study showed highly statistically significant difference between poorly (grade III) and moderately differentiated (grade II) adenocarcinomas with **P-value 0.03** and between poorly (grade III) and well differentiated (grade I) adencarcinomas with **P-value 0.001 (Table 2).**

Table 2: diffusion restriction parameters in different types of rectal adenocarcinoma

Grades of adenocarcinoma	Diffusion status		Grade III versus grade II adenocarcinoma		Grade III versus Grade I adenocarcinoma	
	True Restriction	T2 shin-through	Kendall Tau	P- value	Kendall Tau	P-value
Grade I	**8 (100 %)**	**0 (0%)**	**-0.783**	**0.03**	**-0.657**	**0.001**
Grade II	**3 (81 %)**	**(19%)**				
Grade III	**3 (50 %)**	**3 (50%)**				

The diffusion study showed 81% sensitivity, 76% specifity and positive predictive value and 100% negative predictive value.

All the patients were subjected to ADC value estimation with 8 were well differentiated (grade I), 16 were moderately differentiated (grade II) and 6 were poorly differentiated adenocarcinoma (grade III). Comparing the absolute values of the estimated ADC, the mean ADC value of grade I adenocarcinoma was about 0.855, grade II was about 0.922 and grade III was about 1.4 (No diffusion restriction as false negative result) **(Fig. 3)**.

There was no statistically significant difference in characterization of grade III and normal surrounding tissues.

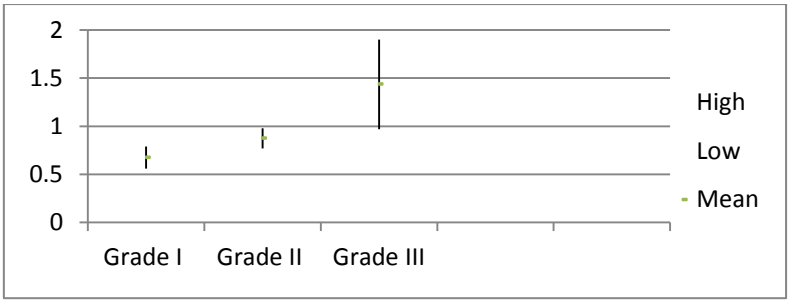

Figure 3: tumor characterization using ADC values.

DISCUSSION

Colorectal cancer is the second most common cancer in women and the third most common cancer in men worldwide. In recent years, mortality rates have decreased due to major changes in therapeutic management, in particular the standardization of the operative procedure and more important accurate pre-operative strategy making is depending on imaging [8].

Around 40–50% of colorectal cancers are located in the rectum. Rectal cancer is defined as a tumor whose margin measured with the rigid rectoscope is 16 cm or less from the anocutaneous line [9].

American Cancer Society considers that the survival of patients with colorectal cancer depends, largely, on the stage of the disease at diagnosis. Thus, in patient with localized disease, 5 years survival is approximately 60%. On the other hand, patients with distant metastasis have 5 years survival rate of less than 10% [10].

Survival relates directly to the extent of the extramural spread into the mesorectum and the ability to achieve surgical clearance at the circumferential resection margins. Two treatment modalities are considered to have a substantial effect on reducing the frequency of local recurrence and improving survival; TME surgery and neoadjuvant chemo-radiotherapy. Preoperative radiation therapy was found to result in down staging and cause the primary tumor to shrink, permitting sphincter preserving surgery and avoidance of colostomy [11].

Imaging for rectal cancer staging is useful to determine which surgical technique would be more appropriate. Ideal imaging modality should accurately assess the depth of tumor penetration (T), lymph node involvement (N), presence of distant metastatic disease (M), mesorectal fascia involvement and anal sphincter involvement [12].

MRI is currently one of the most accurate non-invasive modalities for staging rectal carcinoma. The introduction of phased-array coil MRI and development of T2-weighted fast-spin sequences have enabled accurate determination of prognostic factors and anatomic assessment of the pelvis by delineating rectal tumors through increases in spatial and contrast resolution (Fig. 4), also the lack of peristalsis make the rectum an ideal organ for imaging with MRI [13].

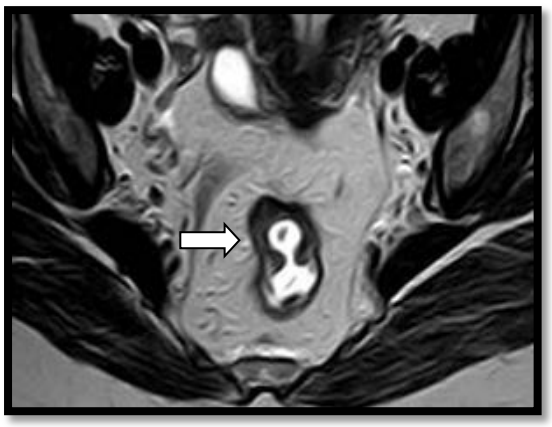

Figure 4— 48 years old female with upper rectal cancer. Axial T2-weighted imaging showing uneven circumferential mural thickening, the outermost part of the mass is about 1.5 cm from mesorectal fascia anteriorly.

Due to its ability to detect and characterize tumors, diffusion weighted imaging (DWI) was increasingly incorporated into standard magnetic resonance imaging (MRI) protocols for tumor imaging [14].

In our study, important technical points done, one of them was the proper angulation perpendicular to the rectal wall at the level of the tumor as improper angulation might give rise to false results regarding the depth of transmural invasion, relation of tumor to mesorectal fascia as well as to other pelvic organs. This technical pitfall was avoided as **Laghi *et al.*** [15] reported.

We included 30 patients with primary rectal cancer and focused on evaluating the role of

DWI in assessing aggressiveness of this malignancy.

19 out of 30patient (63.3%) were found to have lesions located at the lower rectum which is mostly agreed with the study done by **Akasu *et al.*** [16] which revealed 73.5% at the lower third of rectum**.**

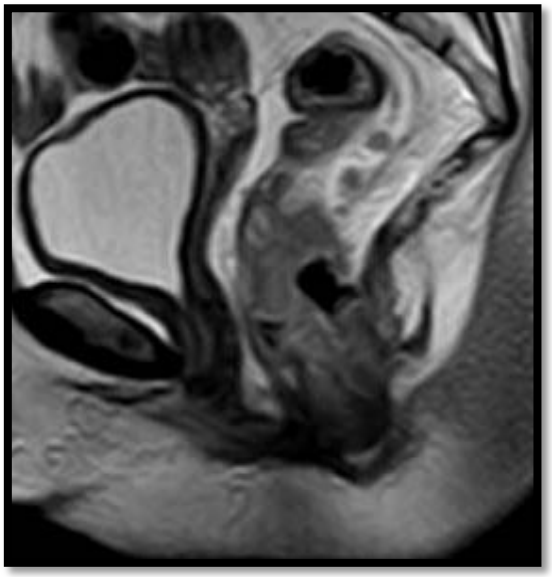

Figure 5—51 years old female with ano-rectal cancer. Sagittal T2-weighted imaging showing lower rectal neoplastic mass with infiltration of the anal canal.

Adenocarcinomas account for all the cases of rectal cancer in our study. Mucinous adenocarcinoma was diagnosed in 6 patients out of 30 by histopathological assessment, which represents 20 % of the cases, this disagree with study done by **Chang *et al*** [17] which revealed that the percentage of mucinous adenocarcinoma 33.6%. This difference might be because their study included a larger number of patients.

With the use of high resolution T2WI, it was possible to evaluate the tumor margins in relation to the layers of tissue in the rectal wall. The determination rests on visualization of a complete zone of hyperintense submucosa between the tumor and the outer hypointense muscularis propria [18].

(Tx) primary tumor cannot be assessed, (T0) no evidence of primary tumor, (Tis) carcinoma in situ: intra-epithelial or invasion of the lamina propria, (T1) tumor invades submucosa, (T2) tumor invades muscularis propria, (T3) tumor invades through the muscularis propria into the subserosa or into the non-peritonealized pericolic or perirectal tissues and (T4) tumor directly invades other organs, structures and/or perforates visceral Peritoneum [19].

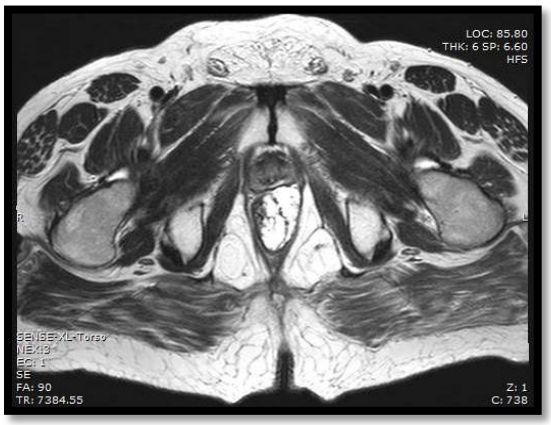

Figure 6—54 years old male with ano-rectal cancer. Axial T2-weighted image shows circumferential mural thickening of rectal wall infiltrating muscularis propria.

Regarding the role of conventional MRI sequences in differentiating T2/T3/T4 staging, our study revealed 83.3%, 87.5% and 50%, respectively with total agreement 73.6 % correlated with histopathology which was totally agreed with the study done by **Karatag *et al.*** [20] which reveled 73.5% total agreement of correlation between MRI and histopathology.

The most frequent diagnostic error caused by MRI consisted in in-correctly differentiation of T2 from early T3 lesions: this over staging was often caused by the presence of desmoplastic reaction within the peri-tumoral tissues that made it difficult for the MR to differentiate between peri-rectal fat spiculation, caused by fibrosis alone from those containing viable tumor cells [21].

By using a cutoff value of 1.20×10-3 mm2/sec, **Khong *et al.*** [22] reported that ADC values had 100% negative predictive value for distinguishing between well and poorly differentiated adenocarcinomas. The increased ADC values likely result from tumor edema, cellular damage, and cell death, which lead to necrosis. Increased vascular permeability and interstitial volume also contribute to their increased ADC values.

Our study revealed that, tumors with low cellularity (eg, mucinous adenocarcinoma) may not have diffusion restriction on DWI; such tumors may also have relatively high ADC values. Even that interpreting diffusion weighted images in conjunction with anatomic images and

employing b-value sequences helps reduce false-negative findings.

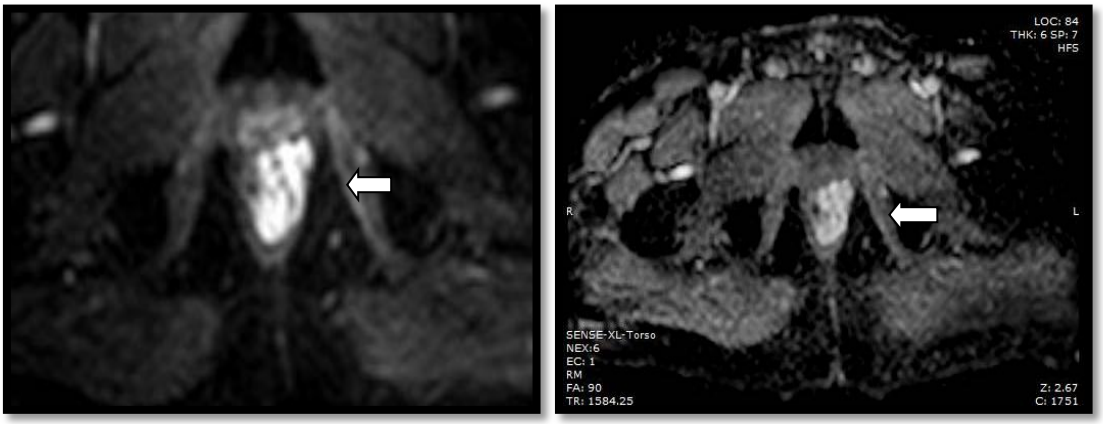

Figure 7—54 years old male with ano-rectal cancer. Axial DW imaging showing circumferential rectal wall thickening with high signal intensity in DW presenting T2 shin-through, ADC value: 2.1x10`-3 mm2/s.

(Nx) regional lymph nodes cannot be assessed, (N0) no regional lymph node metastasis, (N1) metastasis in 1–3 regional lymph nodes and (N2) metastasis in >3 regional lymph nodes.

T2WI was the best sequence to visualize internal morphology of normal node. It was a common misunderstanding that all lymph nodes of high signal intensity contain fat, while fat replacement of nodes is well identified in inguinal and axillary nodes, but in perirectal lymph nodes the high signal is assumed to represent fluid within lymphoid follicles surrounded by a low signal intensity capsule. Recently, many studies have focused on MRI with lymph node specific contrast agents like Ultra-small super paramagnetic iron oxide (USPIO), these studies revealed promising results [23].

Regarding the role of conventional MRI sequences in differentiating N0/N1 staging, our study revealed 83.3% and 50%, respectively with total agreement 66.5 % correlated with histopathology which agrees with the study done by **Zhang *et al.*** [24] which reveled 63.7% total agreement of correlation between MRI and histopathology.

Regarding the role of in the MRI detection of MRF invasion, in agreement with **Giusti *et al.*** [25], our study concluded that preoperative MRI prediction of histologically involved MRF is very accurate with sensitivity and specificity values of 96.3 % and 83.3%, respectively.

CONCLUSION

However MRI has a great value in achieving the best treatment strategy through accurate staging of rectal cancer, prediction of negative CRMs and involvement of the peri-rectal and pelvic LNs. Results of our study demonstrated that the tumors with low cellularity (eg, mucinous adenocarcinoma) may not have diffusion restriction on DWI; such tumors may also have relatively high ADC values. So DWI has a limited role in assessing aggressiveness of rectal cancer, especially in the cases of poorly differentiated adenocarcinoma, in addition has misleading (False negative) results. DWI could be applied for follow up and re-staging of histopathologically proven rectal cancer cases.

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