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ORIGINAL ARTICLE

Role of Apparent Diffusion Coefficient in Evaluation of Rectal Cancer Aggressiveness

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ABSTRACT

Background: This study aims to evaluate the importance of diffusion-weighted MRI imaging (DWI) as a truthful marker for detection of rectal cancer tumor aggressiveness, by studying the relation between apparent diffusion coefficient (ADC) values of the tumors, MRI findings and pathological factors for prognosis. **Methods:** Between October 2017 and May 2019, the study included 80 patients have been proved to have carcinoma of the rectum by colonoscopic biopsy and histopathological assessment. All patients were assessed prior to surgery and neo-adjuvant therapy with standard MRI and diffusion weight images. **Results:** The mean ADC values are lower with poor prognostic factors for tumors with high CEA levels more than 5 ng/ml (P = 0.004), positive nodal disease (P = 0.0001), positive LVI invasion (P = 0.0001), with increasing T stage (P = 0.0001) and significantly lower among poorly differentiated tumors (P = 0.0341). There is also a significant positive correlation (r = 0.487; P = 0.0001) between ADC values and the distance from the tumor to the MRF. **Conclusion**: Our study suggests that quantitative measurement of ADC values can be used in preoperative assessment of degree of rectal cancer progression. ADC is capable of becoming a realistic imaging biomarker of tumor profile aggressiveness.

Keywords: Rectal carcinoma; magnetic resonance imaging; diffusion weighted imaging; ADC value.

INTRODUCTION

Cancer rectum, which is usually adenocarcinoma, involves last 15 cm of the colon distally measuring from the anal verge and it is one of the main reasons of death related to cancer globally [1]. Rectal cancer is difficult to diagnose, it has no specific symptoms during its early stages, making the disease easy to overlook or confuse with other diseases. Although new technology has increased the early diagnostic rate of rectal cancer, most patients still have progressed to late stage disease at diagnosis, leading to poor prognosis [2]. Magnetic resonance imaging (MRI) is considered to be of the best ways to evaluate rectal cancer correctly. MRI and other techniques of imaging are important clinical tools for non-invasive preoperative diagnosis [3] which has important influence in directing the therapeutic course for patients diagnosed with rectal cancer. MRI has the benefit of defining tumor progression through the evaluation of tumor staging and the evaluation of the tumor's association with adjacent tissue subjects, which also guides the course of therapy [4]. Currently, the utilization of diffusion-weighted imaging (DWI) integrated into the protocol of conventional MR is rising gradually due to its confirmed advantage not only for detection of the tumor and its classification but also for tracing response of the therapy [5-8]. Diffusion weighted imaging measures water diffusion characteristics, and by quantifying and expressing these characteristics as an apparent diffusion coefficient (ADC), DWI could be used as an imaging biomarker for better selecting patients with unfavorable prognosis who will benefit from a neoadjuvant treatment which could be more aggressive [9]. Since rectal tumor aggressiveness is demonstrated by several variables , including T-stage, N-stage, mesorectal fascia infiltration (MRF),

carcinoembryonic antigen (CEA), grade of tumor differentiation, and lymphangiovacular invasion (LVI), [10-15]. We goal to evaluate the importance of DW-MRI as demonstrated by the calculated ADC values as a prospective non-invasive tumor aggressiveness biomarker in rectal tumors.

METHODS

During the period from October 2017 to May 2019, the research was conducted in hospitals of Zagazig University. This research included 80 patients confirmed pathologically to be rectal carcinoma (59 males and 21 females) aged from (49 to 69 years old). Inclusion criteria were Pathologically (biopsy) proven rectal carcinoma, accessibility of the surgical specimens pathology repots and accessibility of primary studies for MRI staging including DWI. Exclusion criteria were patients received chemotherapy or radiotherapy, operated cases and patients with hemodynamic or respiratory instability.

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Scanning protocol

The research was done with 1.5-T MR system (Philips Achieva) using phased-array surface coils, while the patient was in supine position the surface coil was placed on the pelvis. The imaging protocol used was the standard one which consists of T2-weighted (T2W) fast spin echo in three orthogonal directions, which were used for clinical staging, axial images done with (repetition time/echo time (TR/TE):5794/137 ms; flip angle: 90; echo train length: 30; number of slices: 22; ,coronal T2WI with (TR/TE):5794/133 ms ,echo train length:30 ,FOV:26, sagittal T2WI with (TR/TE) (5753/134) ms, ETL:30. T1weighted images sequence parameters: TR 500 ms TE 28 FOV= AP 265 RL 340 mm, voxel size RL 1.1 mm AP1.3, slice thickness 5 mm, transverse slice orientation. The axial DWI was performed at b values of 0, 500 and 1000 s/mm^2 with TR/TE: 5245/70 ms using single shot echo planar imaging (EPI). The post-contrast sequences (axial oblique, coronal oblique, and sagittal oblique) all are parallel to the rectum direction. The coronal sequence of T2W was angled alongside the axis of the tumor.

ADC Evaluation

The mean rectal mass ADC was calculated by placing various areas of concern (ROIs) within the tumor in successive parts of the images (identified as restricted areas on ADC map corresponding to its isotropic DWI) and then calculation of the mean ADC was done.

Prognostic Factors

The clinical patient database included clinical, radiological and pathological prognostic variables. At the moment of diagnosis, the clinical variable was plasma level of CEA (ng/mL). At primary staging, these parameters were recovered from MRI: mrT (mrT1-2, 3, 4) and mrN (mrN0, 1, 2) both reported according to TNM staging system and MRF status either free or invaded. The histopathological assessment of the surgical samples was the chief reference for pathological parameters, grades of tumors differentiation and LVI. The pathologist scored the lesion differentiation level according to the levels used in our association: 0, poor; 1, poor to moderate; 2, moderate; 3, moderate to good; 4, good. LVI has been reported to be lacking or existent. The distance from the outermost portion of the lesion to the MRF was also evaluated on the main staging MRI studies for T3 tumors to detect extramural development.

Statistical analysis

Data from historical, clinical, laboratory and outcome measurements gathered coded, reordered, evaluated using Microsoft Excel. Data have been subsequently exported into the software for analysis in the Statistical Social Science Package (SPSS version 20.0). Several tests were used as Chi square test (X2), kappa test, t-test, ANOVA, and Pearson's correlation coefficient; P value was established at <0.05 for significant results & <0.001 for high significant outcome

RESULTS

Our study included 80 patients their age's ranged from 49 to 69 years with the mean age 61.07±5.76 years. The majority of the patients were males (59 patients) representing (73.8%), while females were 21 representing (26.3 %) (**Table S1**).

Table 1 presents the correlations between different clinical, radiological and pathological prognostic factors between the different subgroups.

At the time of diagnosis, 31 (38.8%) patients had the levels of CEA <5 ng/mL and 49 (61.3%) had CEA levels >5 ng/mL.

Regarding MRI staging, 25 patients (31.3%) were considered to be T1, 20 (25%) as T2, 20 (25%) as T3 and 15 (18.8%) as T4. Based on DWI staging, we had 25 patients (31.3%) as T1, 26 (32.5%) as T2, 14 (17.5%) and 15 (18.8%) as T3 and T4 respectively.

From pathological analysis of the specimens, 20 patients (36.3%) proved to be T1, 18 (22.5%) as T2, 22 (27.5%) as T3 and 11(13.8%) as T4. Fifty one patients (63.8%) were staged as N0, while 29 (36.3%) had positive nodal disease (N1 or N2). As regard tumor differentiation, 11 patients (13.8%) had poorly differentiated, 44 (55%) moderately differentiated and 25 (31.3%) good differentiated tumors. LVI invasion was absent in 73 patients (91.3%) and it was present in 7 (8.8%).

Tumor staging was assessed via imaging scans (MRI and DWI) and pathological examinations. From analysis of results, there was significant association and agreement regarding MRI staging with P value <0.0001 and kappa agreement 0.58, while there was more association and agreement regarding DWI staging with P value <0.001 and kappa agreement 0.81 (f **2**).

Correlation between ADC and different prognostic factors

The mean tumor ADC for the whole patients was 1.14±0.13 x 10^{-3} mm^2/s. ROC curve of ADC detection for diagnosis of rectal cancer (**Figure 1**) had an AUC of 0.876 (P < 0.001, **Table 3**) and cutoff value of 0.99 × 10^{-3} mm^2/s with sensitivity = 87.8% and specificity = 95.5%.

Mean ADCs were different significantly for patients with CEA more than 5 ng/ml versus those with CEA less than 5 ng/ml (*P* = 0.004, **Table S2**), mrN0 versus mrN+ (*P* = 0.0001), present LVI invasion versus absent invasion (*P* = 0.0001), for patients having tumors limited to the rectal wall (T1 or T2) versus those having lesions growing beyond rectal wall (T3 and T4, *P* = 0.0001), and for poor differentiated tumors versus moderate or good differentiated ones at pathology (*P* = 0.0341, **Table S3**).

The mean ADCs values are lower with poor prognostic factors for tumors with high CEA levels more than 5 ng/ml, positive nodal disease, positive LVI invasion, with increasing T stage and significantly lower among poorly differentiated tumors (**Figures 2,3,4**).

There was a significant positive correlation (r = 0.487; *P* = 0.0001) between the values of ADC and the distance from the tumor to the MRF (**Figure S1**).

Table 1. Correlations between different clinical, radiological and pathological prognostic factors

		N	%
CEA	**<5**	**31**	**38.8**
	>5	**49**	**61.3**
MRI stage	**T1**	**25**	**31.3**
	T2	**20**	**25.0**
	T3	**20**	**25.0**
	T4	**15**	**18.8**
DWI stage	**T1**	**25**	**31.3**
	T2	**26**	**32.5**
	T3	**14**	**17.5**
	T4	**15**	**18.8**
Pathological staging	**T1**	**29**	**36.3**
	T2	**18**	**22.5**
	T3	**22**	**27.5**
	T4	**11**	**13.8**
LN	**-VE**	**51**	**63.8**
	+VE	**29**	**36.3**
LVI	**-VE**	**73**	**91.3**
	+VE	**7**	**8.8**
Differentiation	**Good**	**25**	**31.3**
	Moderate	**44**	**55.0**
	Poor	**11**	**13.8**
	Total	**80**	**100.0**

CEA=carcinoembryonic antigen; LN= lymph node; LVI =lymphangiovascular invasion

Table 2. Performance of magnetic resonance imaging (MRI) and diffusion weighted imaging (DWI) in rectal cancer diagnosis.

				Pathological stage				Total	X^2	P	Kappa agreement
				T1	T2	T3	T4				
MRI stage	**T**	**T1**	**N**	**21**	**4**	**0**	**0**	**25**	**93.9**	**0.0001**	**0.58**
			%	**72.4%**	**22.2%**	**0.0%**	**0.0%**	**31.2%**			
		T2	**N**	**8**	**12**	**0**	**0**	**20**			
			%	**27.6%**	**66.7%**	**0.0%**	**0.0%**	**25.0%**			
		T3	**N**	**0**	**2**	**14**	**4**	**20**			
			%	**0.0%**	**11.1%**	**63.6%**	**36.4%**	**25.0%**			
		T4	**N**	**0**	**0**	**8**	**7**	**15**			
			%	**0.0%**	**0.0%**	**36.4%**	**63.6%**	**18.8%**			
DWI stage	**T**	**T1**	**N**	**25**	**0**	**0**	**0**	**25**	**161.7**	**0.001**	**0.81**
			%	**86.2%**	**0.0%**	**0.0%**	**0.0%**	**31.2%**			
		T2	**N**	**4**	**18**	**4**	**0**	**26**			
			%	**13.8%**	**100.0%**	**18.2%**	**0.0%**	**32.5%**			
		T3	**N**	**0**	**0**	**14**	**0**	**14**			
			%	**0.0%**	**0.0%**	**63.6%**	**0.0%**	**17.5%**			
		T4	**N**	**0**	**0**	**4**	**11**	**15**			
			%	**0.0%**	**0.0%**	**18.2%**	**100.0%**	**18.8%**			
Total			**N**	**29**	**18**	**22**	**11**	**80**			
			%	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**			

Table 3. Efficiency of apparent diffusion coefficient (ADC) detection in diagnosis of rectal cancer.

AUC	Cutoff	P	95% Confidence Interval		Sensitivity	Specificity
			Lower Limit	Upper Limit		
0.876	**<0.99**	**0.001**	**0.650**	**1.000**	**87.8%**	**95.5%**

AUC= Area under curve

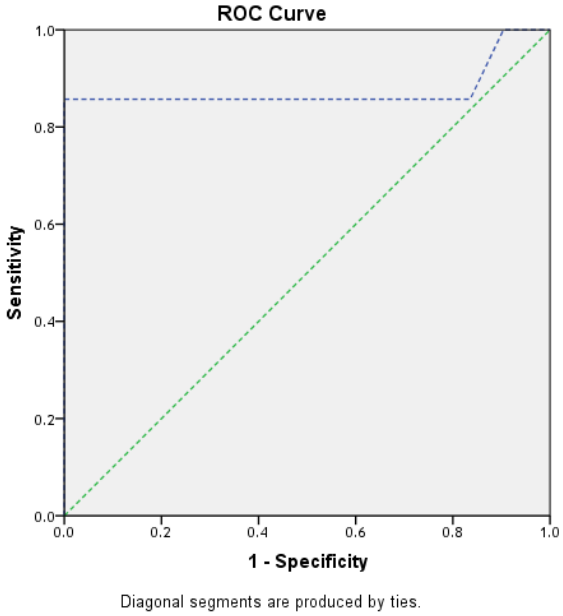

Figure 1: Receiver operating characteristics (ROC) curve of apparent diffusion coefficient (ADC) detection in diagnosis of rectal cancer.

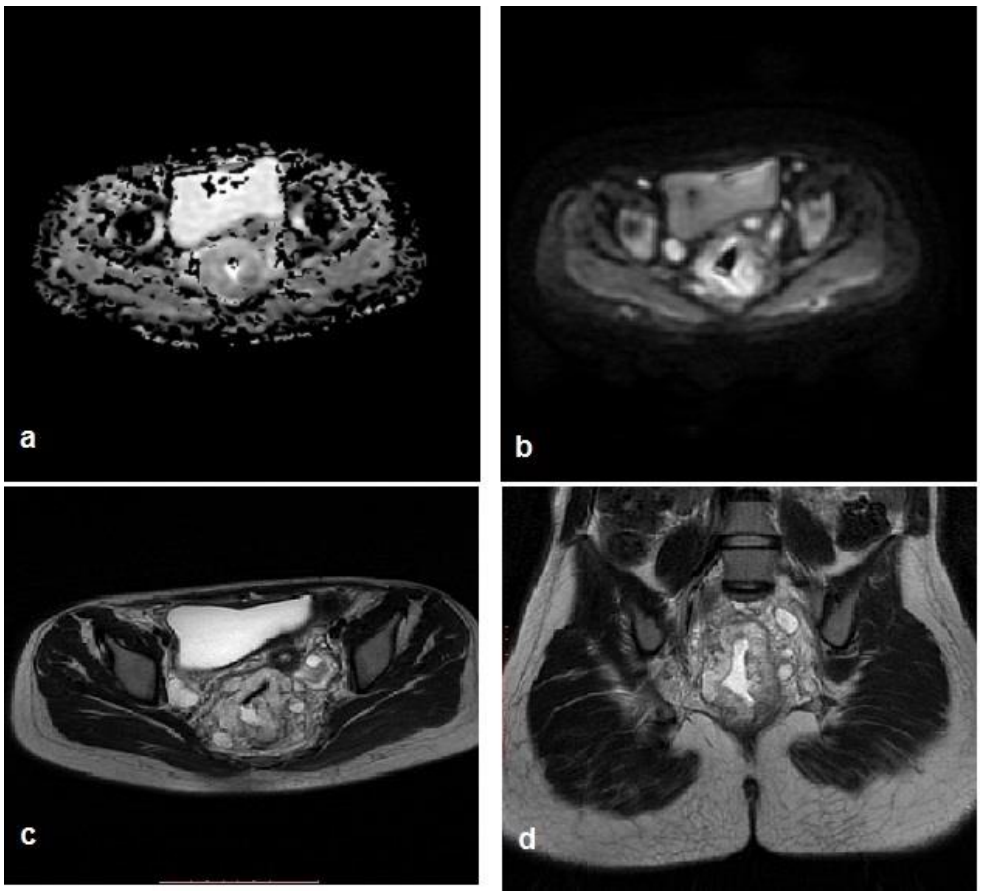

Figure 2. Aggressive rectal neoplasm, staged as T3N2, involving mesorectal fascia and associated with multiple enlarged mesorectal lymph nodes. ADC value was 0.84 x10 mm^2/s. a. ADC map; b. High b-value (b = 1000 s/mm^2) DWI image; c. Axial T2WI and d. Coronal T2WI.

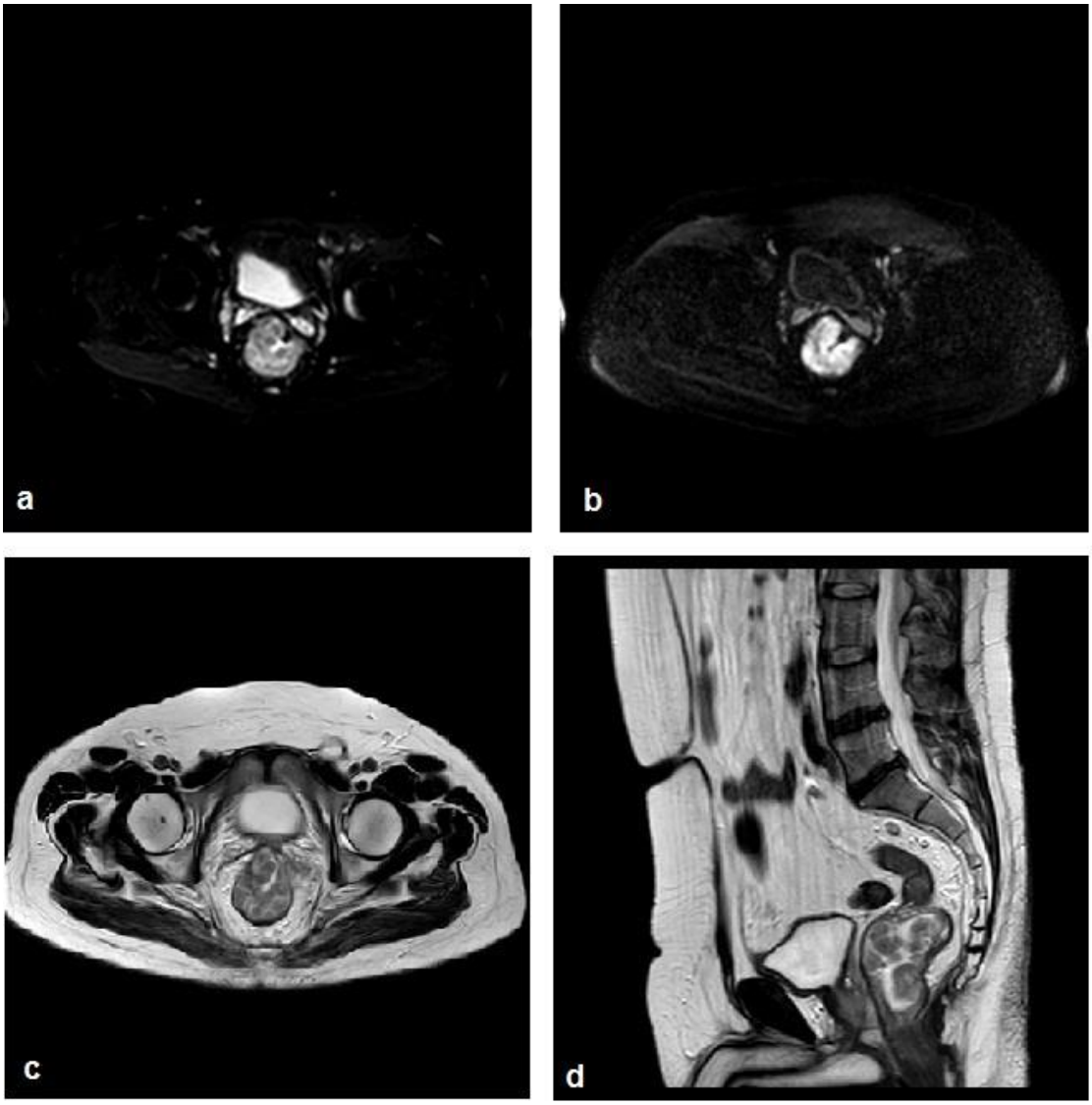

Figure 3. Rectal neoplasm, staged as T2N1, limited to rectal wall, associated with two enlarged mesorectal lymph nodes. ADC value = 1.12 x 10 mm^2/s. a. ADC map; b. High b-value (b = 1000 s/mm^2) DWI image; c. Axial T2WI and d. Sagittal T2WI.

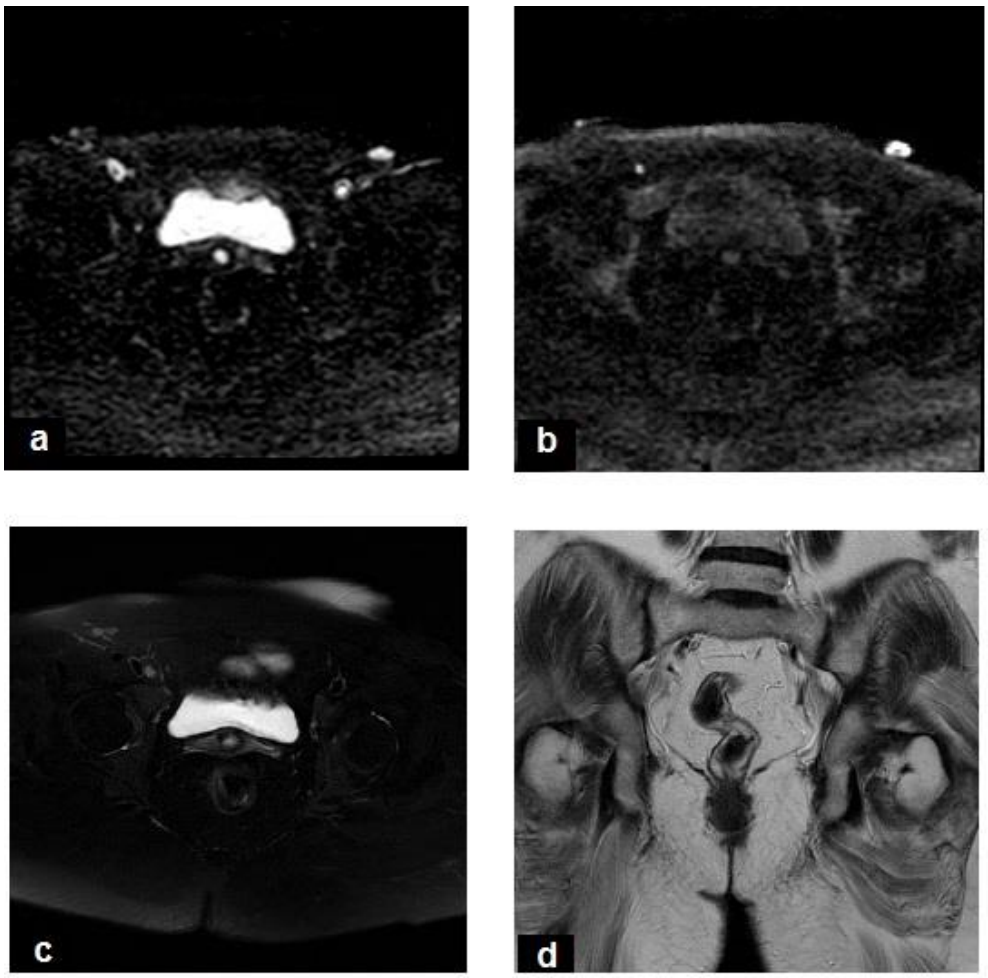

Figure 4. Small polypoidal rectal neoplasm, staged as T1No, not invading muscularis and not associated with mesorectal lymph nodes. ADC value = 1.24 x 10 mm^2/s. a. ADC map; b. High b-value (b = 1000 s/mm^2) DWI image; c. Axial T2WI fat sat and d. Coronal T2WI

DISCUSSION

Rectal cancer is one of the most prevalent tumors in the world and one of the most common gastrointestinal tract malignancies [16]. MRI has been the most precise method for staging of cancer rectum throughout the previous years [17]. DWI becomes more and more essential in evaluation of malignant tumors. It is believed that DWI makes it possible to characterize tissues noninvasively according to their water diffusion properties [18].The main purpose of this research is to assess the significance of DW-MRI as a prospective noninvasive tumor aggressiveness imaging biomarker in rectal cancer.

Recent study results show statistically significant association and agreement more in DWI stage than MRI stage for diagnosis of rectal carcinoma, this is in agreement with Jiang et al [19] who stated that qualitative and quantitative data provided by DWI has higher diagnostic value and can be an important adjunct diagnostic method for rectal cancer. AUC of ADC for diagnosis of rectal carcinoma was 0.876 with cut off level <0.99 (P value <0.001), this is going with Jiang et al [19] who found that ROC curve of ADC detection for diagnosis of rectal cancer had an AUC of 0.995 (P<0.05) and cut off value of 0.935×10^{-3} mm^2/s .

The mean value of ADC for all groups studied was 1.14±0.13, this is nearly in correlation with Semedo et al[20] who stated that mean tumor ADC for the entire population of the patients was 1.069 ± 0.162 $x10^{-3}mm^{2/}s$.

In this research ADC in patients with positive nodal disease was significantly reduced, with considerable positive correlation between ADC and lesion distance to MRF (r = 0.487, p = 0.0001) this is in alignment with

Semedo et al [20] who encountered that the mean ADC for lesions with MRF involvement or lesions associated with nodal metastasis was considerably reduced with significant positive correlation (r = 0.374; P = 0.019) between the values of ADC recorded and the distance of the lesion to the MRF respectively. Also this was in a line with Wieder et al who proved that prognosis worsening is correlated with a gradual growth in the tumor extension depth in the mesorectal fat surrounding it.

Semedo et al [20] had proven that both invasion of MRF and lymph nodes metastasis are strong predictors of recurrence and remote metastases. Therefore, the existence of any correlation between ADC and MRF or nodal status indicates that ADC correlates with prognosis on its own. This could be clarified by the reality that ADC values are indirectly obtained from the cellular microarchitecture of a tumor and can therefore represent the lesion aggressiveness. This is further strengthened by finding that less differentiated tumors showed comparatively lesser ADCs, indicating again that low ADC values are associated with an unfavorable tumor profile. This was in agreement with Gu et al [12] who concluded that poorly differentiated tumors had low ADC values and this was in alignment of our study which concluded that ADC is lower with increasing T stage and significantly lower among poorly differentiated tumor with P values <0.0001 and 0.0341 respectively.

The recent research concluded that ADC was significantly lower among patients with CEA>5 and in patients with LVI with P values <0.004 and <0.0001 respectively, this was in controversy with Semedo et al [20] who resulted that there was no significant correlation existed between ADC and CEA pretreatment levels, or LVI presence in pathology.

Our research had some limitations. First, our ADC measurements were achieved by evaluating three sample ROIs that may not be completely representative of the whole lesion [21]. However, this method has been selected because it is very time-consuming and hard to describe the entire tumor extent in clinical practice. Second, MRI examination is considered to be a truthful method for the cancer rectum staging, its evaluation is observer-dependent and may have happened under- or overstaging. Finally, evaluating the aggressiveness of lesions using outcome parameters like disease-free or overall survival would have been clinically interesting; however, this would involve a bigger cohort study of patients and a longer follow-up period beyond the scope of our present research.

In conclusion, rectal cancer ADC values correlate significantly with prognostic variables, including MRF status, nodal phase and the grades of pathological tumor differentiation. Tumors with MRF invasion, lymph node involvement, less differentiated tumors, lesions infiltrating the rectal wall, CEA concentrations greater than or equal to 5 ng / mL, and those with LVI are the cancers with lower ADC values and poorer prognosis. Our study suggests that ADC is capable of becoming an imaging biomarker of biological tumor profile.

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REFERENCES

1- Kang H, O'Connell JB, Leonardi MJ, Maggard MA, McGory ML, Ko CY. Rare tumors of the colon and rectum: a national review. Int J Colorectal Dis 2007; 22:183–189.

2- Garborg K. Colorectal cancer screening. SurgClin North Am 2015; 95: 979-989.

3- Jhaveri KS and Hosseini-Nik H. MRI of rectal cancer: an overview and update on recent advances. Am J Roentgenol 2015; 205: W42-55.

4- Kim MB, Hong TS and Wo JY. Treatment of stage II-III rectal cancer patients. CurrOncolRep 2014; 16: 362.

5-Koh DM, Padhani AR. Diffusion-weighted MRI: a new functional clinical technique for tumor imaging. Br J Radiol 2006;79: 633–635.

6- Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol 2007;188:1622–1635.

7- Patterson DM, Padhani AR, Collins DJ. Technology insight: water diffusion MRI a potential new biomarker of response to cancertherapy. Nat ClinPractOncol 2008;5:220–233.
8- Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, et al. Diffusion weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia 2009;11:102–125.
9- Lambrecht M, Deroose C, Roels S, Vandecaveye V, Penninckx F, Sagaert X, et al. The use of FDG-PET/CT and diffusion-weighted magnetic resonance imaging for response prediction before, during and after preoperative chemoradiotherapy for rectal cancer. ActaOncol 2010;49:956–963.
10-Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, BourneMW, Williams GT. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging.Br J Surg 2003;90:355–364.
11. Huh JW, Oh BR, Kim HR, Kim YJ. Preoperative carcinoembryonic antigen level as an independent prognostic factor in potentially curative colon cancer. J SurgOncol 2010;101:396–400.
12. Gu J, Khong PL, Wang S, Chan Q, Law W, Zhang J. Quantitative assessment of diffusion-weighted MR imaging in patients with primary rectal cancer: correlation with FDG-PET/CT. Mol Imaging Biol 2011;13:1020–1028.
13-Ho ML, Liu J, Narra V. Magnetic resonance imaging of rectal cancer. Clin Colon Rectal Surg 2008;21:178–187.
14. Wieder HA, Rosenberg R, Lordick F, Geinitz H, Beer A, Becker K, et al. Rectal cancer: MR imaging before neoadjuvant chemotherapy and radiation therapy for prediction of tumor-free circumferential resection margins and long-term survival. Radiology 2007;243:744–751.
15. Lahaye MJ, Engelen SM, Nelemans PJ, Beets GL, van de Velde CJ, van Engelshoven JM, et al. Imaging for predicting the risk factors-the circumferential resection margin and nodal disease-of local recurrence in rectal cancer: a meta-analysis. Semin Ultrasound CT MR 2005;26:259–268.
16-Rania A. Marouf , Mary Y. Tadros , Tarek Y. Ahmed. Value of diffusion-weighted MR imaging in assessing response of neoadjuvant chemo and radiation therapy in locally advanced rectal cancer. EJRNM 2015;46, 553–561
17-Valentini V, Aristei C, Glimelius B, Minsky BD, Beets-Tan R, Borras JM, et al. Multidisciplinary rectal cancer management. In: 2nd European rectal cancer consensus conference (EURECA-CC2) radiotherapy oncol 2009;92(2):148–163
18- Dzik-Jurasz A, Domenig C, George M, Wolber J, Padhani A, Brown G, et al. Diffusion MRI for prediction of response of rectal cancer to chemo radiation. Lancet 2002;360:307–8.
19- Hua Jiang, Xin-Chun Xiao, Yong Yu, Jing-Hua Liang, Yi-Qiang Xie. Value of magnetic resonance and diffusion-weighted imaging for diagnosis and assessment of rectal cancer. Int J Clin Exp Med 2016;9(6):10579-10585
20- Curvo-Semedo L, Lambregts DM, Maas M, Beets GL, Caseiro-Alves F, Beets-Tan RG. Diffusion-Weighted MRI in Rectal Cancer: Apparent Diffusion Coefficient as a Potential Noninvasive Marker of Tumor Aggressiveness .journal of magnetic resonance imaging 2012;35:1365–1371.
21- Hinrich A. Wieder, Robert D Rosenberg, Florian L ordick, Hans Geinitz, Ambros J. Beer, Karen A. Becker, et al. Rectal cancer: MR imaging before neoadjuvant chemotherapy and radiation therapy for prediction of tumor-free circumferential resection margins and long-term survival. Radiology 2007;243:744–751.

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