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Role of Diffusion Weighted Imaging in Assessing Aggressiveness of Rectal Cancer: An Institution Based Cross Sectional Study

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ABSTRACT

High resolution MRI (Magnetic Resonance Imaging) is the imaging modality of choice in staging rectal carcinoma and in planning optimal treatment. Diffusion weighted imaging (DWI) helps in tumour detection, characterization and evaluating treatment response. The diffusion restriction is quantified as apparent diffusion coefficient (ADC). The study aims to determine if pre treatment ADC is useful in predicting extramural invasion, nodal metastases, circumferential resection margins, lymphovascular emboli and histological tumour grading thus predicting tumour aggressiveness. The study was a retrospective study conducted in a tertiary oncological referral institute. Patients with carcinoma rectum referred to the department for MRI during the period of a year from November 2018 to October 2019 were included in the study. The final study group included 38 patients of carcinoma rectum. The apparent diffusion coefficient was calculated and its association with the tumour grade, T stage, nodal metastases, circumferential resection margin and lymphovascular emboli was evaluated according to pathology reports retrospectively collected from the patient records. Mean ADC among Grade 1 tumor was 1.130, among Grade 2 tumor was 0.859 and among Grade 3 Tumor was 0.629. Mean ADC was low (0.798) in Advanced T Stage compared to early stage (1.043). Mean ADC was low in those with metastatic lymph nodes and with positive lymphovascular emboli. In our study there was significant association of mean ADC with tumor differentiation grade, transmural involvement by tumor, presence of nodal metastases and lymphovascular emboli with lower ADC being associated with features of aggressive neoplasm.

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Key Words
Rectal carcinoma, diffusion weighted imaging, apparent diffusion coefficient, aggression, prognosis

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INTRODUCTION

High resolution MRI (Magnetic Resonance Imaging) is the imaging modality of choice in staging rectal carcinoma. MRI also helps in planning optimal treatment and helps decide whether upfront surgery or preoperative neoadjuvant therapy would benefit a particular case. It predicts the circumferential resection margin accurately and it also predicts subserosal extension and lymphadenopathy better than the other available modalities[1].

The prognosis of rectal cancer depends on various factors like the T stage of tumor, invasion of mesorectal fascia the presence and number of metastatic lymphadenopathy the histopathological grading of the tumor and presence of lymphovascular emboli[2-4].

The availability and acceptance of neoadjuvant therapies viz radiotherapy and chemotherapy in managing patients with rectal carcinoma has increased the need for identifying patients with aggressive disease who could benefit from these modalities to reduce the rate of local recurrence[5,6].

Diffusion weighted imaging (DWI) has gained its rightful place in routine evaluation of carcinoma rectum in many centers as it helps in tumor detection, characterization and also helps in evaluating treatment response[7]. Diffusion weighted imaging measures water diffusion, which are in turn determined by cell density, vascularity, viscosity of extracellular uid and cell membrane integrity[8]. The diffusion restriction is quantified as apparent diffusion coefficient (ADC), which in turn can possibly predict tumor aggression. In a study done by Sabry *et al.*[9] the mean ADC value correlated with tumour histologic grade in cases of colorectal cancer. In a study done by El-Kader *et al.*[10], it was inferred that ADC had limited role in assessing aggressiveness of rectal cancer especially in the cases of poorly differentiated adenocarcinoma. Hence literature review suggests that the role of ADC in identifying tumour aggressiveness is not clear, further there are no studies in India regarding the same.

This study aims to determine if pre-treatment ADC can be useful in predicting extramural invasion, nodal metastases, circumferential resection margins, lymphovascular emboli and histological tumor grading, thus help in stratifying patients who have a high risk for recurrence and can benefit from aggressive pre surgical neoadjuvant therapy.

MATERIALS AND METHODS

The study was a retrospective, institutional based study conducted in a tertiary oncological referral institute. The study period was of a year from November 2018 to October 2019. The ethical committee approval was waived off for the study as the study was retrospective. The patients who were referred to the department of radiology within the study period were enrolled in the study. Initially 50 patients were enrolled for the studies in them 12 patients were excluded as they did not meet the inclusion criteria. Finally 38 patients were enrolled for the study.

The inclusion criteria were:

- Histologically proven cases of carcinoma rectum.
- Treatment was by surgical excision of tumor
- Post operative availability of resected surgical specimen for analysis of tumor differentiation grade, confirmation of lymphatic and vascular emboli, mesorectal fascia status, T stage and nodal positivity status

The exclusion criteria were:

- Patients with any contraindication for MR imaging.
- Claustrophobic patients
- Patients who had already undergone neoadjuvant therapy before MR imaging which can change the ADC values or patients with recurrence
- Patients with mucinous tumors which are known to alter the ADC values making it higher due to the mucin content[11]

The final study group included 38 patients (23 male and 15 female). The median age group of the study population was 47 years (Age range from 19 to 70 years).

Patients were imaged in a 1.5 Tesla MRI scanner using a phased array surface coil. The sequences performed were T2-weighted Fast spin echo in axial, coronal and sagittal planes, T1-weighted image in axial plane, Diffusion weighted image using EPI with B values 0, 500 and 1000. Axial plane was planned perpendicular to tumor long axis and coronal plane parallel to tumor long axis (Fig. 1). Patients were not given intravenous contrast, antispasmodics, bowel preparation or rectal distension.

Apparent diffusion coefficient was calculated as a mean of ROI (region of interest) placed in three different sections to include as much of solid portion of tumor as possible.

The association of ADC was then evaluated with the tumor grade (grade 1: Well differentiated, grade 2: Moderately differentiated and grade 3: Poorly differentiated), T stage (early-T1 and T2: Advanced T3 and T4), nodal metastses (positive or negative) Circumferential resection margin (positive or negative) and lymphovascular emboli (positive or negative) all on histopathological examination.

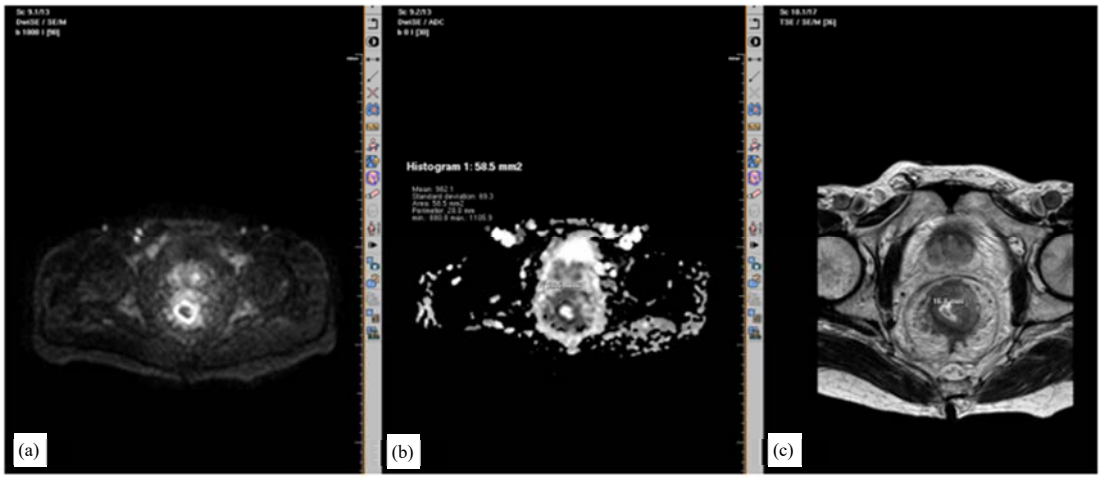

Fig. 1(a-c): Original, (a) Rectal wall thickening which is hyperintense in Diffusion imaging (B1000), (b) Apparent diffusion coefficient map shows corresponding hypointensity, (c) T2 weighted image shows hyperintense rectal wall thickening

Statistical analysis: Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables. ANOVA (Analysis of Variance) was the test of significance to identify the mean difference between more than two groups for quantitative and qualitative data respectively.

p-value (probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyse data.

RESULTS

The final study group included 38 patients (23 male and 15 female). The median age group of the study population was 47 years (Age range from 19-70 years). There was significant association of mean ADC with respect to Tumor grade, T stage (early and advanced), nodal metastases and lymphovascular emboli. The association of mean ADC with circumferential resection margins (CRM) status was not statistically significant.

Distribution of Tumor grade, T stage, N Stage, CRM (circumferential resection margin) and lymphovascular emboli among subjects in our study is shown in Table 1.

Association of apparent diffusion coefficient values with respect to Tumor Grade is shown in Table 2.

Table 1: Distribution of tumor grade, t stage, N stage, CRM and lymphovascular emboli among subjects (original)

	Counts	Percentage
Tumor grade		
Grade 1 (well differentiated)	10	26.3
Grade 2 (moderately differentiated)	19	50.0
Grade 3 (poorly differentiated)	9	23.7
Total	38	100.0
T stage on HPE (Histopathological examination)		
Early (T1 and T2)	12	31.6
Advanced (T3 and T4)	26	68.4
N (nodal) status on HPE		
Positive	19	50.0
Negative	19	50.0
CRM on HPE		
Positive	4	10.5
Negative	34	89.5
LVE on HPE		
Positive	11	28.9
Negative	27	71.1

Association of apparent diffusion coefficient values with respect to Tumour stage, Nodal status, Circumferential resection margin status and Lymphovascular emboli is shown in Table 3.

Mean ADC among grade 1 tumor was 1.130±0.131, among Grade 2 tumor was 0.859±0.072 and among grade 3 Tumor was 0.629±0.040. There was significant difference in mean ADC with respect to Tumor grade. Mean ADC was low (0.798) in Advanced T Stage compared to early stage (1.043). Mean ADC was low in those with metastatic lymph nodes (0.762) compared to Negative nodal status (0.989). Mean ADC was low in those with lymphovascular emboli [LVE] (0.711) positive compared to Negative LVE (0.943) on histopathological examination.

DISCUSSIONS

Diffusion weighted imaging is useful in identifying responders from non responders to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer[12]. It also has a role in characterization

Table 2: Association of apparent diffusion coefficient value with respect to tumor grade (original)

Tumor grades	Mean ADC ($\times10^{-3}$ mm^2 sec^{-1}) value	Standard deviation	p-value
Grade 1	1.13	0.13	<0.001*
Grade 2	0.85	0.07	
Grade 3	0.63	0.04	

#ANOVA test was used for test of significance, p<0.05 was considered statistically significant and $ADC: Apparent diffusion coefficient

Table 3: Association of ADC value with respect to T stage, N status, CRM status and LVE (original)

ADC value ($\times10^{-3}$ mm^2 sec^{-1})	Mean	SE	Minimum	Median	Maximum	p-value
T stage						
Early	1.043	0.184	0.76	1.03	1.30	<0.001*
Advanced	0.798	0.155	0.57	0.82	1.20	
Total	0.876	0.199	0.57	0.85	1.30	
N stage						
Positive	0.762	0.130	0.57	0.78	0.97	<0.001*
Negative	0.989	0.193	0.65	0.96	1.30	
Total	0.876	0.199	0.57	0.85	1.30	
CRM on HPE						
Positive	0.773	0.285	0.62	0.64	1.20	0.278
Negative	0.888	0.188	0.57	0.88	1.30	
Total	0.876	0.199	0.57	0.85	1.30	
LVE on HPE						
Positive	0.711	0.121	0.58	0.65	0.97	0.001*
Negative	0.943	0.186	0.57	0.91	1.30	
Total	0.876	0.199	0.57	0.85	1.30	

#Independent t test was used for test of significance, p<0.05 was considered statistically significant, $ADC: Apparent diffusion co efficient, CRM: Circumferential Resection Margin and LVE: Lymphovascular emboli

and identification of residual disease after neoadjuvant treatment hence it is already included in the standard protocol of rectal imaging in most centres.

The present study aimed at ascertaining if diffusion weighted imaging(by calculating ADC) was able to assess the degree of aggressiveness in rectal carcinoma. Our study demonstrated a significant association between ADC with extramural invasion, Nodal metastases, tumor grade and lymphovascular emboli. The association between ADC and CRM positivity was not statistically significant.

Several studies have identified the factors which herald the poor prognosis in carcinoma rectum namely extramural invasion, mesorectal fascia involvement (CRM positivity), poor differentiation of tumors and presence of lymph nodal metastases[3,10,13]. It would be beneficial if some test could help predict these factors so that the patients who need more aggressive therapy may be identified.

DWI-MRI explores the random Brownian motion of water molecules in intracellular and extracellular space and measuring water motion, reflects the biological changes in the tumour microenvironment[14]. ADC is an indicator of cellularity of the tumor and the membrane permeability

A study by Sabry *et al*.[9] has indicated that ADC values correlated with tumour histological grade in colorectal cancers. According to their study the poorly differentiated tumor had an ADC of 0.979×10^{-3} mm^2 sec^{-1}, moderately differentiated tumour had an ADC of 1.112×10^{-3} mm^2 sec^{-1}, well differentiated tumor had an ADC of 1.273×10^{-3} mm^2 sec^{-1}. There was a statistically significant similar observation in our study where the tumor grade correlated with the ADC where the ADC was least in the poorly differentiated tumors and highest in the well differentiated tumors.

In our study there was association between T stage (early tumors with no extra mural invasion and advanced tumors with extension into mesorectal fascia) and ADC values. Curvo-semedo *et al.*[15] have made a similar observation in their study where tumors limited by bowel wall had higher ADC (mean ADC 1.148×10^{-3} mm^2 sec) compared to tumors extending beyond bowel wall (mean ADC 1.046×10^{-3} mm^2 sec^{-1}).

However, there was no significant association with CRM positivity and ADC in our study, which was similar to the observation made by Akashi *et al.*[16] where they compared the ADC values calculated on 3 T MRI to CRM and did not find a significant correlation.

Presence of nodal metastases is an important independent prognostic factor in local recurrence and distant metastases.In our study there was a significant association of presence of nodal metastases with ADC. The cases with nodal metastases had lower mean ADC values. These observations are similar to the observations by Curvo-semedo *et al*.[15] where they too identified a significant correlation of ADC with lymph nodal metastatic status with node positive patients having a mean ADC of 1.148×10^{-3} mm^2 sec^{-1} and node negative patients mean ADC of 1.028×10^{-3} mm^2 sec^{-1}.

In our study there was significant association of lymphovascular emboli with ADC values, however, significant association was not identified by Curvo-Semedo *et al*.[15], But their study depicted lower mean ADC (1.029×10^{-3} mm^2 sec^{-1}) in LVE present cases to (1.105×10^{-3} mm^2 sec^{-1}) LVE absent cases. Further larger study may clarify wether the association is significant or merely positive.

LIMITATIONS OF THE STUDY

Our study had a smaller sample size of 38 patients. In our study 8 patients underwent neoadjuvant treatment after MRI in such cases we correlated their pre treatment ADC with tumor status in pathological specimens of post operative cases, the neoadjuvant therapy might have altered the disease status in these patients varying the results. In our setup patients who have aggressive disease may not be the only ones who present with advanced disease because the patients who have less aggressive disease may also present late due to economic and social constraints.

The results need to be validated with larger multicentric studies. Similar studies in same socio economic scenario may provide further clarity on application of these findings in our practice.

CONCLUSION

In our study there was significant association of mean ADC with tumor differentiation grade, transmural involvement by tumor, presence of nodal metastases and lymphovascular emboli with lower ADC being associated with features of aggressive neoplasm viz poorly differentiated tumor, transmural involvement by tumor, presence of lymphnodal metastases and lymphovascular emboli. Hence ADC can be a reliable predictor of tumor aggression and patients with lower tumor ADC may benefit more from more aggressive management.

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