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Complete Response to Neoadjuvant Chemoradiation in Locally Advanced Rectal Cancer: Will DW MRI Hold the Key to Deciding Non Surgical Management?

Authors
Dr Sumod Mathew Koshy MD, FRCR, Dr Anil Prahladan DNB, EDiR, Dr Sonia Abraham MD, Dr Krishnankutty Nair Ramachandran MD
Division of Imageology, Regional Cancer Centre, Medical College Campus, Trivandrum, Kerala India Pin 695011
Corresponding Author
Dr Sumod Mathew Koshy MD, FRCR
Division of Imageology, Regional Cancer Centre, Medical College Campus, Trivandrum, Kerala, India PIN 695011
Email: *sumodmk@gmail.com, +91 471 252 2604, +91 9446810833*

Abstract
Rectal carcinomas are among the more common malignancies diagnosed worldwide in both genders. Over the last couple of decades, MRI has gradually replaced transrectal ultrasound and CT as the imaging modality of choice in staging of rectal carcinoma. Of late, several studies have been conducted to assess the feasibility of conservative or non surgical management of carcinoma rectum. Patients who show complete pathological response, post chemoradiation may benefit from an organ preserving approach. Multiparametric MR, in addition to its pre eminent role in staging, also plays an important role in the post treatment setting. Our study was designed to assess the ability of DWI in predicting complete pathological response to neoadjuvant chemoradiation in locally advanced carcinoma rectum, to examine the need for MR imaging in the setting of post neoadjuvant chemoradiation and to evaluate the role of DWI in staging of carcinoma rectum. Receiver operating characteristic curves and area under curve (AUC) analysis of multiple variables showed that AUC of ADC_{mean} was higher. Cut off ADC values were also calculated applying Youden's statistics. Applying the cut off ADC_{max} of $\leq 1.53 \times 10^{-3}$ mm^2/s , complete and partial responders were accurately predicted with a sensitivity of 73.33% and specificity of 86.67%. Our study shows that DW imaging if done properly, can predict complete pathological response with reasonably good accuracy thus obviating the need for aPET – CT and also reduce the frequency / or, increase the interval between scopy and biopsy during follow up. Quantitative Diffusion Weighted MR Imaging can potentially provide a single non invasive test to determine complete pathological response and thus decide treatment strategy.

Introduction

Rectal carcinomas are among the more common malignancies diagnosed worldwide in both genders.[1] These tumours are potentially curable, depending upon the stage at time of detection. Although the primary method of diagnosis is through a scopy and biopsy, imaging has a major role in the staging work up. Over the last couple

of decades, MRI has gradually replaced transrectal ultrasound and CT as the imaging modality of choice in staging of rectal carcinoma. Although a curative resection or a combination of neoadjuvant chemoradiation and curative resection form the treatment gold standard at present [2], over the years, the concept of organ preserving therapy has imbibed itself into the management options for rectal carcinoma. The pioneering work in this direction stemmed from seemingly high treatment related morbidity and mortality. Since then, several studies have been conducted to assess the feasibility of conservative or non surgical management of carcinoma rectum. Patients who show complete pathological response (CPR) post chemoradiation may benefit from an organ preserving approach. [3,4,5,6,7] The assessment of CPR includes clinical examination, biopsy confirmation and a multipronged imaging evaluation which includes PET CT and MRI. [8, 9] Multiparametric MR, in addition to its pre eminent role in staging, also plays an important role in the post treatment setting. This versatility of MRI is enhanced by diffusion weighted imaging (DWI) which reflects the cellularity of the tissue being imaged. DWI has widespread applications in oncologic imaging and has been accepted as one of the mainstays of post treatment response assessment. [10] In the post chemo RT setting, normal bowel morphology will be distorted due to fibrosis, making residual tumour assessment difficult with conventional oblique axial T2 weighted images. Earliest treatment response occurs at the cellular level, such as, reduction in cell proliferation rate, increased apoptosis and reduced microvascularity. These are reflected as an increase in tumour ADC. Thus quantitative diffusion weighted imaging can potentially identify residual tumour which exhibits restricted diffusion on a background of post treatment fibrosis [11].

Aims and Objectives

Primary Objective

- To assess the ability of Diffusion Weighted Imaging in predicting complete pathological response to neoadjuvant chemoradiation in locally advanced carcinoma rectum

Secondary objectives

- To examine the need for MR imaging in the setting of post neoadjuvant chemoradiation
- To evaluate the role of Diffusion Weighted Imaging in staging of carcinoma rectum

Materials and Methods

The study was designed as a retrospective observational one. Imaging of 30 patients who fulfilled the following criteria were included in the study.

Inclusion Criteria:

Diagnosed as moderately differentiated adenocarcinoma rectum. A single histological subtype was taken in order to maximise tumour homogeneity among patients and to avoid tissue inherent MR signal differences between different histological subtypes. Similarly mucin secreting adenocarcinomas were also excluded.

Had a pretreatment staging MRI which confirmed locally advanced carcinoma rectum and included DW imaging

Received neoadjuvant chemoradiation according to standard regimen followed by a post chemoradiation reassessment MR that included DW imaging

Underwent radical surgery with total mesorectal excision and Low anterior / Abdominoperineal resection

Histopathological analysis of post operative specimen done

All MR studies were done on 1.5Tesla MR Scanner. Images were obtained using a phased array abdominal coil. Sequences studied included T1W, T2W, DWI + ADC and Post Contrast T1W with emphasis on the oblique axial plane that was planned on the Sagittal T2W images. In all MR

examinations, DW imaging was done with B values 0 and 1000 and the corresponding ADC maps were obtained using standard post processing software. All images were viewed on PACS imaging workstations using 6MP fusion monitors. The final histopathological report of thirty patients (n = 30) who underwent radical surgery after chemoradiation were grouped into two, those with no viable tumour cells (Complete Pathological Response) and those with viable tumour cells (Partial Response). An equal number was taken in both groups in order to increase statistical accuracy. The pre chemoRT and post chemoRT MR images of all thirty patients were studied. The pre chemo RT images were first reviewed in order to confirm the site of tumour and to be used as a guide for identifying the region of interest (ROI) on the post chemoRT images, namely the treated tumour bed. The treated tumour bed was identified on the post chemo RT Oblique Axial T2 images and the section with maximum tumour volume i.e. maximum single wall thickness, was identified (Fig 7). The corresponding DW axial image and ADC maps were then evaluated. Multiple ADC values (atleast three) were obtained from the tumour bed using uniformly sized ROI's. Maximum ADC (ADC_{max}) and Mean ADC (ADC_{mean}) values were obtained for all thirty patients and tabulated. Standard statistical evaluation tools were used and ROC curves obtained for both parameters.

Results

Receiver operating characteristic curves were plotted for each variable and area under curve (AUC) was calculated (Fig. 4 and 5). AUC of ADC_{mean} was higher. Cut off ADC values were also calculated applying Youden's statistics. Applying the cut off ADC_{max} of ≤1.53 x 10^{-3} mm^2/s , complete and partial responders were accurately predicted with a sensitivity of 73.33% and specificity of 86.67%. (Table 1). In most case DW images, despite their inherent low spatial resolution, were able to exquisitely demonstrate foci of residual tumour, even within a single voxel, as illustrated in Figs. 6, 7 and 8.

Figures 9, 10 and 11 illustrate a case of gross residual tumor after chemoradiation.

Figures 12, 13 and 14 show images of a patient with histopathological complete response.

Table 1

Variable	AUC	P Value	Cut off ADC	Sensitivity	Specificity
ADC max	0.798	0.0005	≤1.53	73.33	86.67
ADCmean	0.800	0.0003	≤1.35	80	80

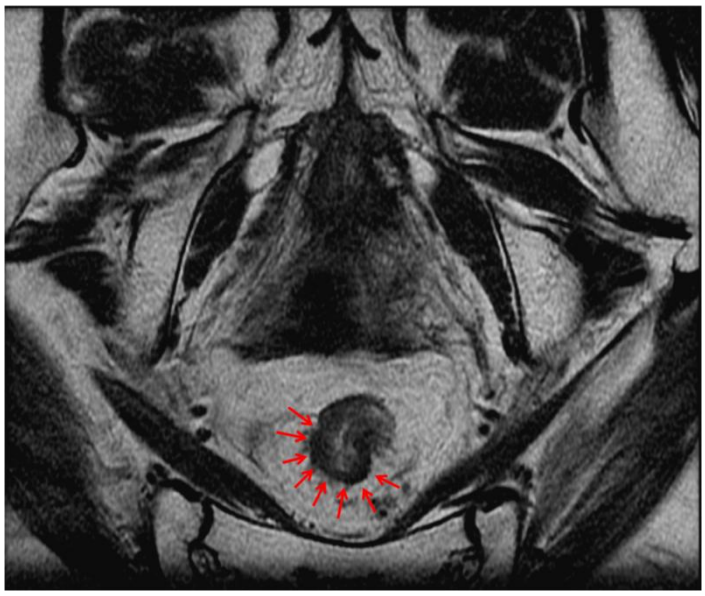

Fig I. Axial T2W image showing (red arrows) post chemo RT tumor bed. Note the low T2 signal which indicates significant fibrosis.

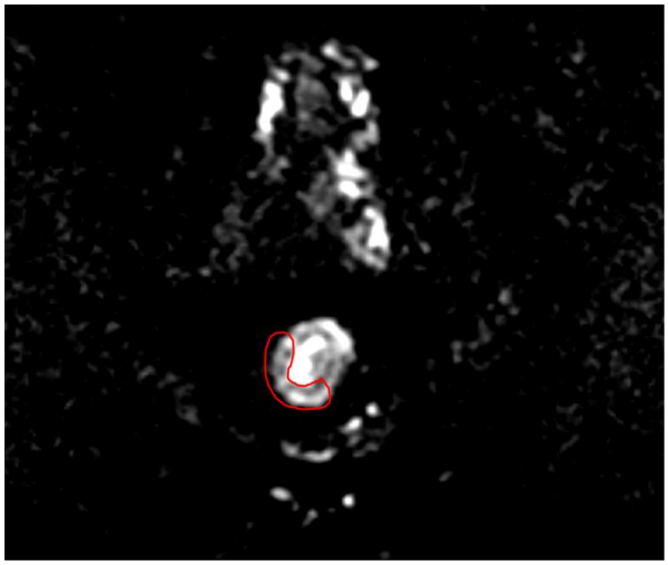

Fig II. Axial DW image corresponding to Fig 1. The area outlined in red denotes the tumour.

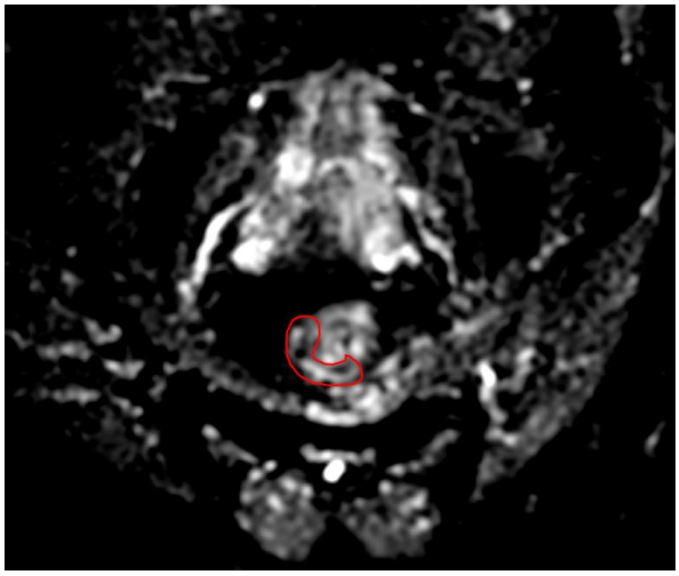

Fig III. ADC map of Fig 2. ROI's were obtained from within the area marked in red.

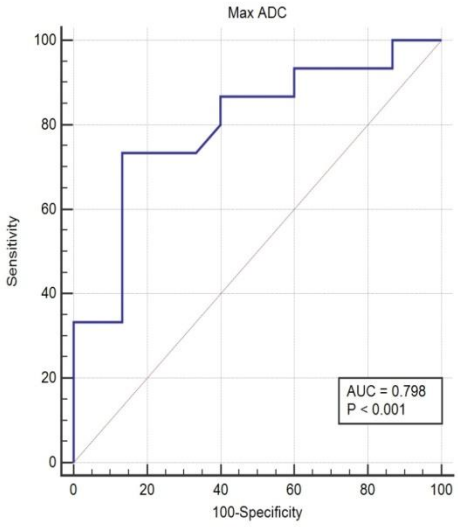

Fig IV.ROC curve of ADCmax values.

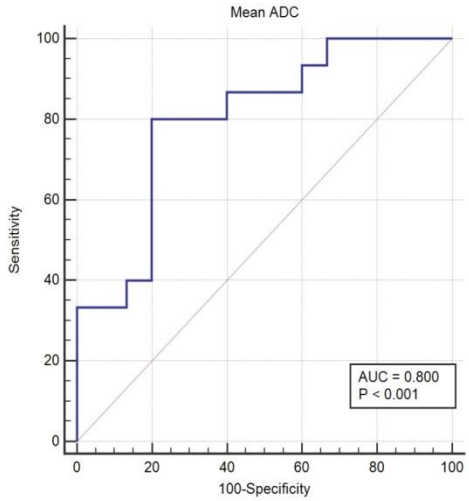

Fig V. ROC curve of ADC mean values.

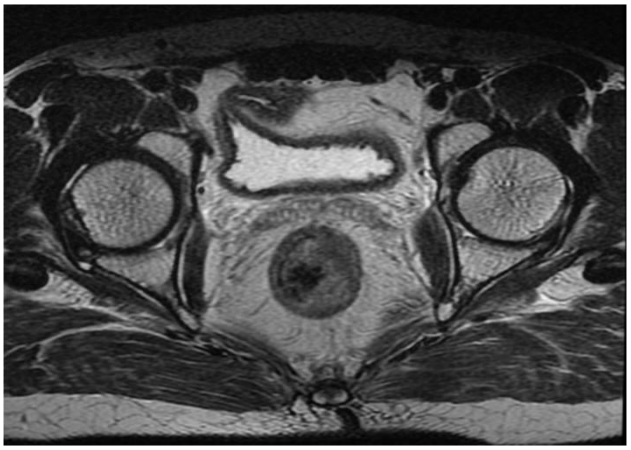

Fig VI. Axial T2W image of a patient with pathological evidence of residual tumour showing the section with maximum single wall thickness.

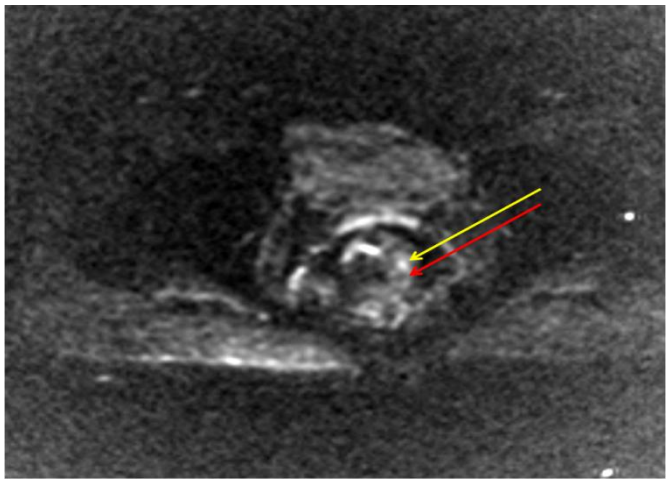

Fig VII. DW image corresponding to Fig 6. The image shows a punctate high signal focus(yellow arrow) adjacent to an area of low signal (red arrow).

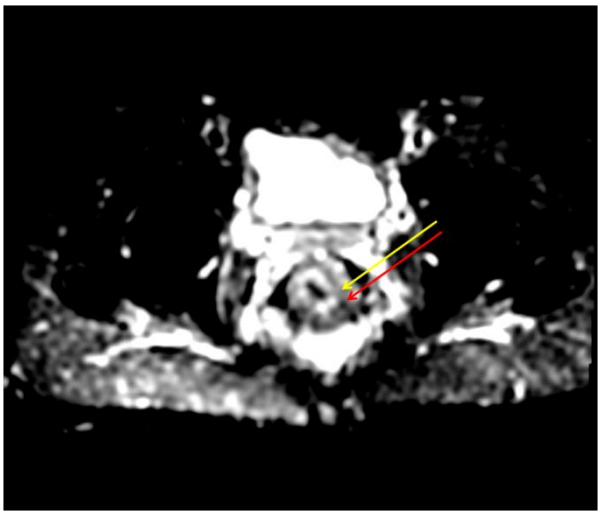

Fig VIII. ADC map corresponding to Fig 7. The colored arrows match the foci seen on the DW image with the yellow arrow pointing to a focus of

restricted diffusion - implying residual tumor. The adjacent low signal on DW shows very low ADC value (red arrow) suggestive of an area of fibrosis. ADCmax and ADC mean were 1.45 x 10-3 mm2/s and 1.18 x 10-3 mm2/s respectively for this patient.

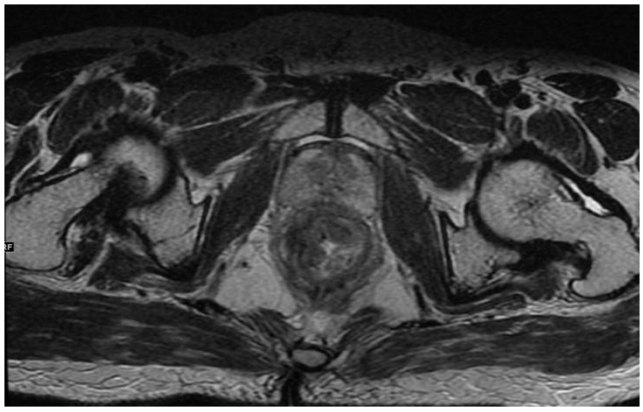

Fig IX. Axial T2W image of a patient with pathological residual tumor showing section with maximum single wall thickness.

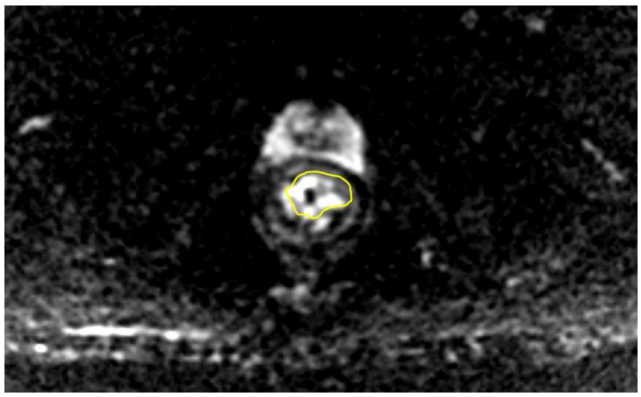

Fig X. Axial DW image corresponding to Fig. 9 showing areas of bright signal (outlined in yellow).

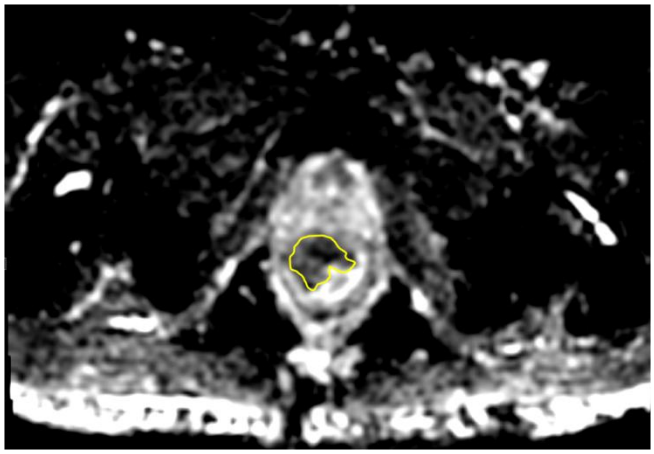

Fig XI. ADC map corresponding to Fig. 10 showing dark areas matching the bright signal on DWI (outlined in yellow) suggestive of restricted diffusion and thereby implying residual disease. The ADCmax and ADC mean values were 1.1 x 10-3 mm2/s and 0.83 x 10-3 mm2/s respectively.

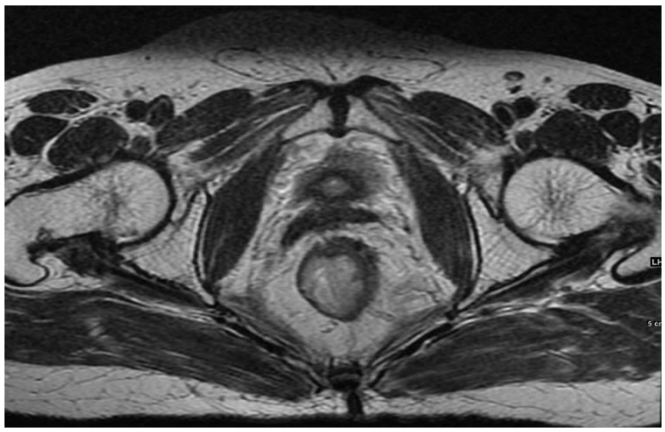

Fig XII. Axial T2W image of a patient with complete pathological response showing the section with maximum wall thickening.

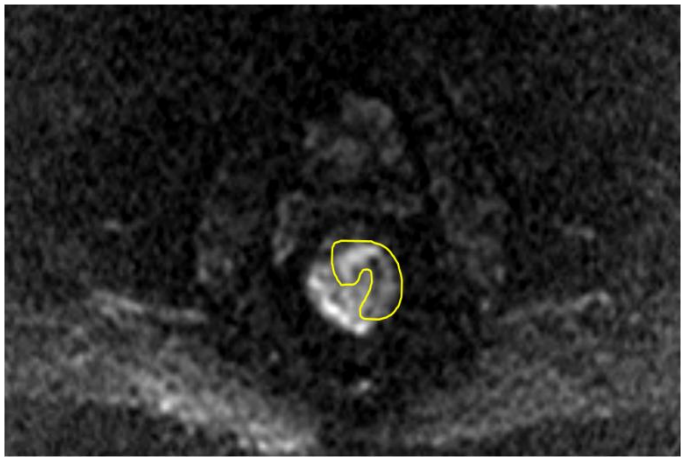

Fig XIII.DW image corresponding to Fig. 12 showing areas of intermediate to low signal (outlined in yellow).

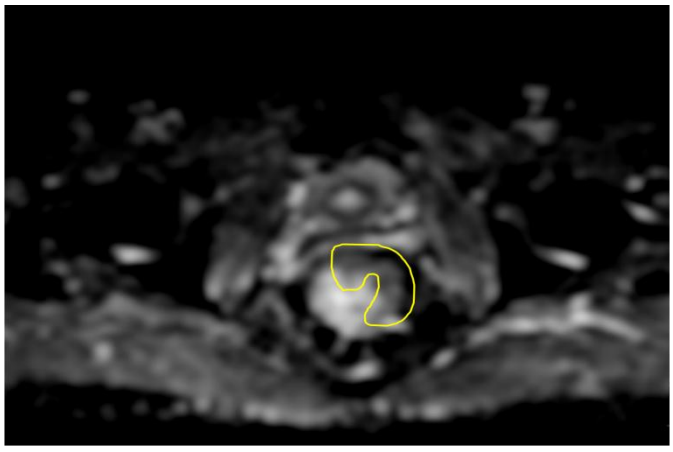

Fig XIV. ADC map corresponding to Fig.13 showing no dark areas in the region of interest (outlined in yellow) and thus low cellularity, thus implying that residual disease is less likely. The ADCmax and ADC mean values were 2.27 x 10-3 mm2/s and 1.65 x 10-3 mm2/s respectively.

Conclusion

Our study shows that DW imaging if done properly, can predict complete pathological response with reasonably good accuracy. This can obviate the need for PET - CT, which is more expensive, less accessible and involves radiation exposure and also reduce the frequency, or, increase the interval between scopy and biopsy during follow up.

Considering the evolving paradigm shift in management of rectal cancer that is currently in vogue, namely an organ conserving approach, accurately determining complete response to chemo RT can have a dramatic impact on patient management.

Quantitative Diffusion Weighted MR Imaging can potentially provide a single non invasive test to determine complete pathological response and thus decide treatment strategy. More studies in this regard are needed for affirming our findings.

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