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Role of apparent diffusion coefficient in assessment of loco-regional nodal spread in cancer rectum: correlative study with histopathological findings

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Abstract

Background Rectal cancer is associated with high morbidity and mortality rates. Preoperative assessment and detection of nodal metastasis are crucial for selecting a proper treatment plan. Diffusion-weighted imaging is considered to be a crucial functional imaging technique that can aid in determining the condition of lymph nodes. This study aimed to assess the diagnostic utility of MRI functional images by use of apparent diffusion coefficient in regional nodal assessment in rectal cancer.

Results This study included 54 patients including 29 males (53.7%) and 25 females (46.3%) presented with pathologically proven rectal cancer. Regarding rectal adenocarcinoma, functional MRI imaging using ADC values found to have a better sensitivity (86.24%) in detection of regional nodal metastasis than conventional morphological MRI criteria with $1.05 \times 10^{-3} \text{ mm}^2/\text{s}$ was employed as cutoff value to distinguish metastatic from non-metastatic lymph nodes with statistically significant *P* value (< 0.001); nevertheless, regarding the accuracy there was no difference (68.52%). As regards mucinous and signet ring cell carcinoma, morphological assessment using conventional MRI sequences were found to have a better accuracy (72.96%) and sensitivity (57.69%) than ADC value, with the latter showed low statistically significant results (*P*-value < 0.201) in distinguishing metastatic and non-metastatic nodes. This could be explained by extremely high ADC values of nodes for these pathological types owing to their high mucin content.

Conclusions MRI functional imaging using ADC values can be utilized to distinguish metastatic from non-metastatic lymph nodes in rectal adenocarcinoma employing diagnostic accuracy of 86.52%. However, morphological assessment using conventional MRI was found to be better in assessment of regional lymph nodes at mucinous and signet ring rectal carcinoma.

Keywords Apparent diffusion coefficient, Rectal cancer, Regional lymph nodes

Background

Regrading cancer diagnosis worldwide, colorectal carcinoma is ranked third [1]

Nodal involvement in rectal cancer is a crucial prognostic indicator because it affects the likelihood of local recurrence as well as overall survival [2].

Today, magnetic resonance imaging (MRI) is used to evaluate lymph nodes status. Metastasis can be present

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in tiny nodes; thus, while the nodal morphological features on MRI standard sequences are frequently used to assess the disease extent, they do not have an acceptable sensitivity and specificity for these evaluations [3].

Diffusion-weighted imaging (DWI) is regarded as a modality of a good significance for tumor detection, prognosis assessment, and treatment response evaluation. Regarding rectal cancer, it has been noted that the ADC values have a good significance in assessing tumoral stages and they can serve as an imaging biomarker for tumor status and aggressiveness [4].

In regional assessment of other malignancies, as mediastinal lymphadenopathy in pediatrics, the value of DWI and ADC to differ metastatic and non-metastatic lymph nodes has been observed. Cell membrane would hinder extracellular water diffusion in highly cellular malignancies, resulting in a lower ADC value. Combining these techniques with morphological criteria, such as lymph node size, contour, and the ratio of long to short axes, considerably increased their performance [5].

Nodal spread is considered to be a significant indicator in prognosis in cancer rectum. Understanding the pathways of lymphatic drainage from various rectal segments, the commonest nodal groups involved as well as the precise localization of these nodes are crucial for proper staging and putting surgical treatment strategies. The mesenteric vessels and the pelvic sidewall vessels both supply to the rectum. Following the path of these arteries is the lymphatic drainage from the rectum [6].

This study aimed to assess the value of functional MRI imaging using apparent diffusion coefficient value in assessment of metastasis in regional nodes in rectal cancer in correlation with histopathological findings.

Methods

This prospective study was approved by the ethics committee on February 2021. The study was done at our institution where the patients were enrolled for a 6-month period from May 2022 to October 2022.

Patients

It included 54 patients with pathologically proven rectal carcinoma referred for pelvic MRI and then had undergone surgical resection and postoperative histopathological analysis.

This study included patients with pathologically proven rectal carcinoma with a treatment plan by surgical resection.

The exclusion criteria involved contraindications for MRI examination, non-neoplastic rectal masses, more than three-week interval between MRI and surgery and presence of motion artifact on the DWIs.

All patients provided their informed consent.

History taking

Including history of altered bowel habit, tenesmus, mucus discharge and fresh rectal bleeding.

Patient preparation

Simple explanation of the procedures was done. The patients were advised to have a warm water enema 1–2 hours before the examination.

MRI examination

MRI protocol The MRI examinations were done in sagittal, coronal and axial projections using an Achieva 1.5 Tesla MRI machine with a body coil with parameters as follows:

- **Axial T1 WIs:** Time of repetition (TR) 436 ms, time to echo (TE) 10 ms, matrix 256×512 , and FOV 250 mm, slices number 25, slice gap 1–2 mm, slice thickness 3 mm, scan duration 1.18 min. Flip angle = 90
- **Sagittal, axial and coronal T2 WIs:** TR 7000 ms, TE 120 ms, FOV 250 mm, thickness of slice 3 mm, slice gap 2 mm, scan duration 1.17 min, flip angle 90°.
- **DWIs:** done in the axial plane (b values 0, 500 & 800 s/mm²).
- **ADC calculation:** Region of interest (ROI) was drawn freehand, keeping it as large as feasible and covering at least two-thirds of the examined lymph node.

MRI images interpretation Morphological evaluation of lymph nodes in various pulse sequences was used to qualitatively interpret MR images, while measuring ADC values was used to quantitatively assess them. Four radiologists collectively recognized the local lymph nodes on the T2WIs (MFA, AAH, SHI, SMMG (clinical experience of 12, 12, 10, and 5 years, respectively, in reading rectal MRI).

Tiny lymph nodes smaller than 2 mm were excluded because it was difficult to manually place the ROI in the center of the lymph node.

- Qualitative assessment

Mesorectal lymph nodes were reviewed by the four radiologists who assessed the morphological features as number, long- and short-axis diameters, outline, T1, T2 signals and comparing them to muscles at same pulse sequence.

- Quantitative assessment

The four radiologists measured the ADC value in each lymph node independently after drawing ROI at the center of the examined LN, and the average was calculated.

Histopathological analysis

The final diagnoses were established by histopathological examination by a pathologist (MEMS with a nine years of experience). The histopathological report quantified the obtained LNs and those that were metastatic. In case all the collected LNs were metastatic, then all identified LNs on corresponding MR images were considered to be metastatic. This rule applied also for non-metastatic LNs.

Statistical analysis

The statistical program SPSS (Statistical Package for the Social Sciences) version 28 was used to code and enter the data (IBM Corp., Armonk, NY, USA). For quantitative data, the mean, standard deviation, median, minimum, and maximum were used; for categorical data, frequency (count) and relative frequency (%) were used. The optimal cutoff value of ADC for the detection of malignancy was discovered using area under curve analysis, which was used to generate the ROC curve. The nonparametric Kruskal–Wallis and Mann–Whitney tests were used to compare quantitative variables. Statistics were considered significant with *P* values under 0.05.

Results

The study included 29 and 25 males and females, respectively, with pathologically proven rectal carcinoma confirmed using endoscopic biopsy. Their ages ranged from 25 to 77 years with a mean age of 52.94 years.

Among 54 patients with rectal carcinoma, total number of 189 lymph nodes was examined by assessing cross-sectional MRI morphological criteria, quantitative and qualitative method using DWIs and ADC value. Then, the results were correlated to the histopathological findings postoperatively.

The examined lymph nodes were grouped into adenocarcinoma and non-adenocarcinoma (mucinous and signet ring cell carcinoma) groups as ADC values of the non-adenocarcinoma subtypes were extremely high owing to their high mucin content.

Regarding quantitative functional assessment of adenocarcinoma group (Figs. 1, 2, 3), the study showed that ADC mean value of the metastatic LNs from adenocarcinoma ($0.85 \times 10^{-3} \text{ mm}^2/\text{s}$) was considerably less than that of non-metastatic LNs ($1.26 \times 10^{-3} \text{ mm}^2/\text{s}$). This yielded statistically significant results (*P*-value < 0.001) with area under the curve (AUC), which was 0.904 with

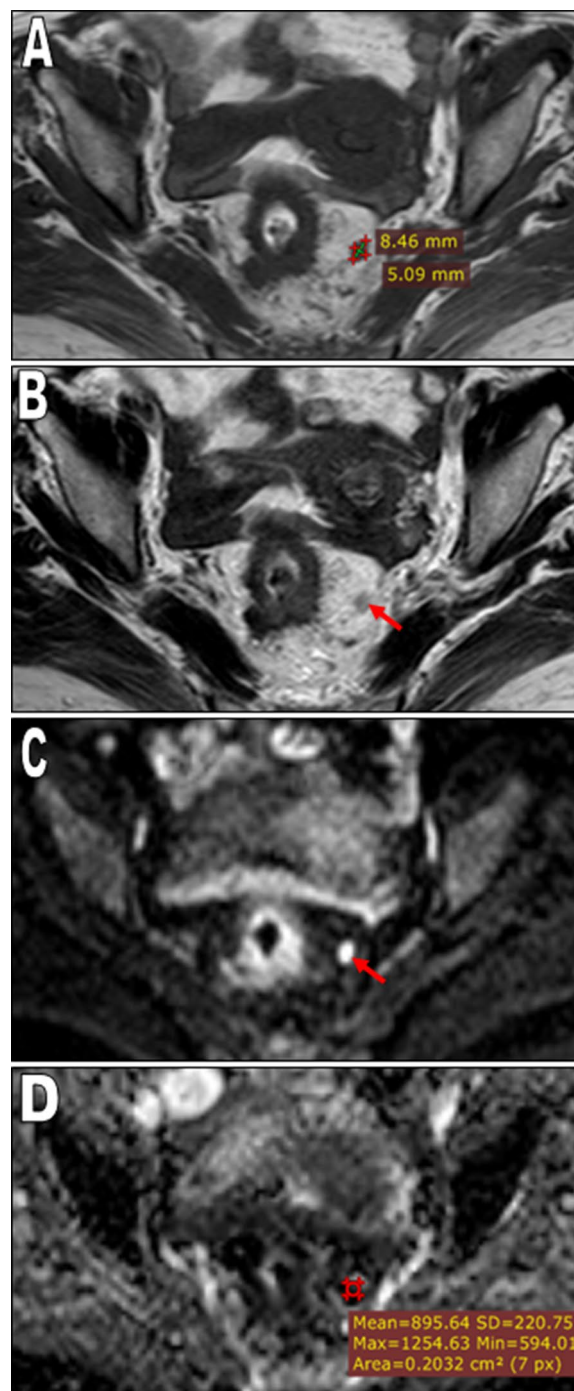


Fig. 1 MRI for a 61-year-old female patient with pathologically proven rectal adenocarcinoma presented clinically by bleeding per rectum. **A** Axial T1 WI and **B** Axial T2 WI showed enlarged left peri-rectal lymph node measuring about 8.5×5.1 mm at maximum axial dimensions, eliciting intermediate T1, heterogeneous high T2 signals, has an oval configuration with irregular borders, morphologically it is considered to be suspicious lymph node **C** DWI and **D** ADC map showed restricted diffusion; with the predominant bright areas on DWI corresponding to low signal areas on the ADC map ADC mean = $0.89 \times 10^{-3} \text{ mm}^2/\text{s}$. Histopathological analysis confirmed metastatic nature of the examined lymph node

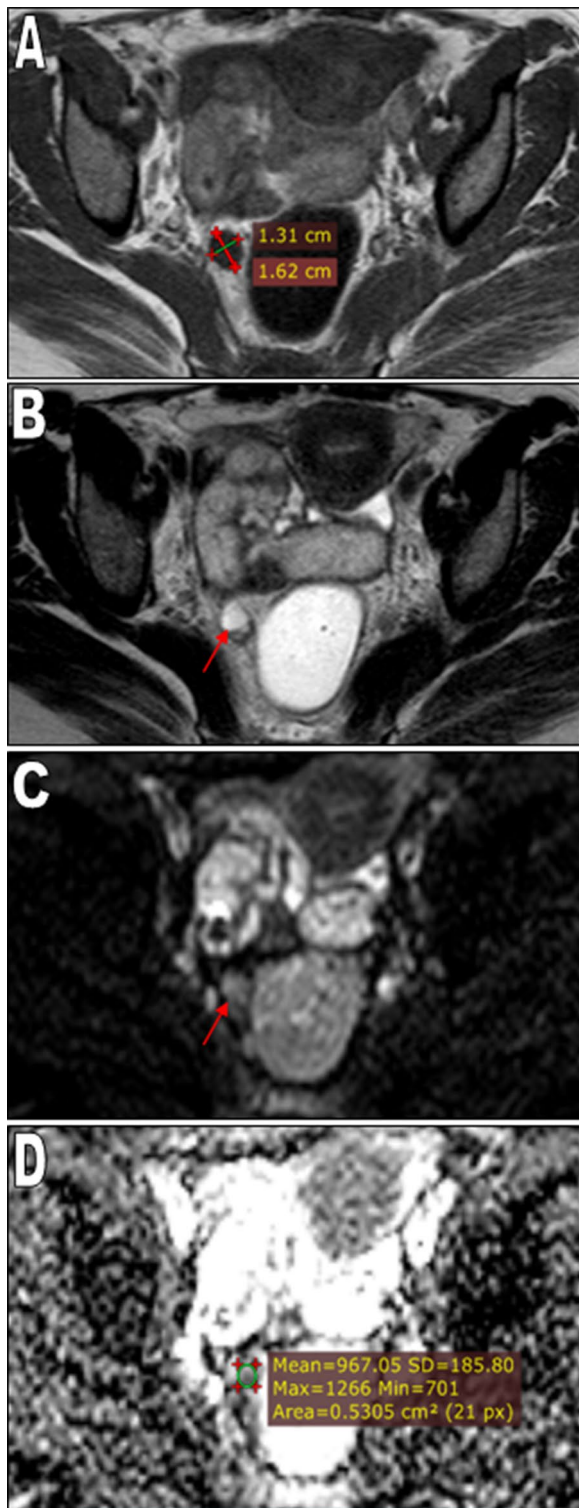


Fig. 2 MRI for a 58-year-old female patient with pathologically proven rectal adenocarcinoma presented clinically with tenesmus and bleeding per rectum. **A** Axial T1 WI and **B** Axial T2 WI showed enlarged right peri-rectal lymph node measuring 16 × 13 mm at maximum axial dimensions, eliciting intermediate T1 and heterogeneous high T2 signals, has an oval configuration with regular borders, morphologically it is considered to be suspicious lymph node. **C** DWI and **D** ADC map showed restricted diffusion, with the predominant bright areas on DWI corresponding to low signal areas on the ADC map ADC mean = $0.96 \times 10^{-3} \text{ mm}^2/\text{s}$. Histopathological analysis confirmed metastatic nature of the examined lymph node

calculated maximum accuracy of 86.52%, sensitivity of 86.4%, specificity of 86.6%, positive predictive value (PPV) of 54.29%, and negative predictive value (NPV) of 97.17% and using $1.05 \times 10^{-3} \text{ mm}^2/\text{s}$ as cutoff value to identify metastatic from non-metastatic LNs.

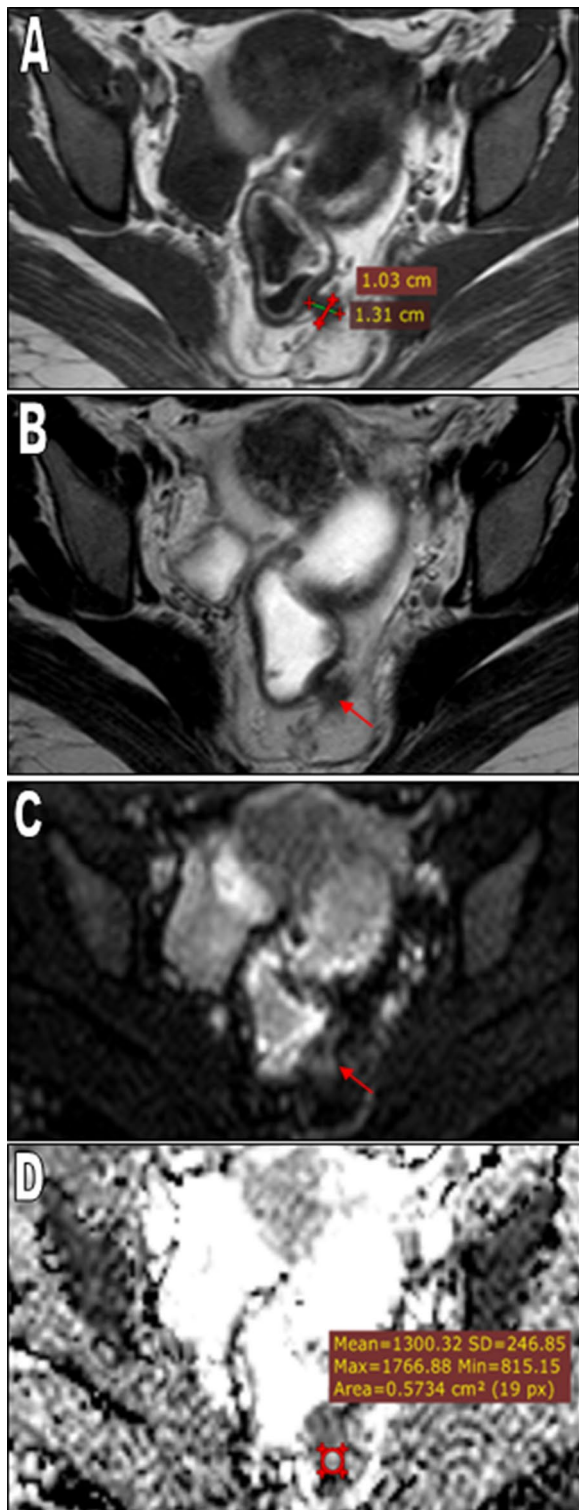
Regarding quantitative functional assessment of non-adenocarcinoma group (Fig. 4), this study found that ADC mean value of the metastatic LNs from non-adenocarcinoma group, mucinous and signet ring cell carcinoma, ($1.55 \times 10^{-3} \text{ mm}^2/\text{s}$) was not lower than of non-metastatic LNs ($1.26 \times 10^{-3} \text{ mm}^2/\text{s}$). For this subtype, these results were of low statistical significance (P -value < 0.201) with AUC, which was 0.394, when maximum accuracy of 50% was calculated, with sensitivity of 26.9%, specificity of 77.3%, PPV of 58.33%, and NPV of 47%, and an ADC value of $1.5 \times 10^{-3} \text{ mm}^2/\text{s}$ was used as cutoff value in order to distinguish between non-metastatic and metastatic lymph nodes.

Morphological assessment of lymph nodes was done by assessing the lymph nodes size (longest diameter of the short axis), margin, shape and signal intensity, and accordingly, all the examined lymph nodes were further categorized into suspicious and non-suspicious, and the results were then correlated to the histopathological findings of the harvested lymph nodes.

Regarding morphological assessment of adenocarcinoma group, maximum accuracy of 86.52% was calculated to distinguish metastatic and non-metastatic lymph nodes with sensitivity of 27.27%, specificity of 97.48%, PPV of 66.67%, and NPV of 87.88%.

Regarding morphological assessment of non-adenocarcinoma group, the results showed sensitivity of 57.69%, specificity of 90.91%, PPV of 88.24%, and NPV of 64.52% with maximum accuracy of 72.69% for distinguishing metastatic and non-metastatic lymph nodes.

Finally, we compared between the morphological and functional assessment to distinguish metastatic and non-metastatic lymph nodes in each group separately and we found that: -



◀ **Fig. 3** MRI for a 31-year-old female patient with pathologically proven rectal adenocarcinoma presented clinically with tenesmus. **A** Axial T1 WI and **B** Axial T2 WI showed enlarged left peri-rectal lymph node measuring about 13×10 mm at maximum axial dimensions, eliciting intermediate T1 and T2 signals, has an oval configuration with irregular borders, morphologically it is considered to be suspicious lymph node. **C** DWI and **D** ADC map showed restricted diffusion; with the predominant bright areas on DWI corresponding to high signal areas on the ADC map. ADC mean = 1.3×10^{-3} mm²/s. Histopathological analysis confirmed non-metastatic nature of the examined lymph node

Regarding adenocarcinoma group (Fig. 5):-

- **Functional assessment** shows accuracy of 86.52% and sensitivity of 86.24%.
- **Morphological assessment** shows accuracy of 86.52% and sensitivity of 27.27%.

Both ADC value and MRI morphological criteria have nearly the same accuracy of 86.52% in detection of metastatic regional lymph nodes with the ADC value, which has a higher sensitivity of 86.4% (compared to 27.27% for morphological criteria) and NPV of 97.17% (compared to 87.88% for morphological criteria).

Regarding non-adenocarcinoma group (Fig. 6): -

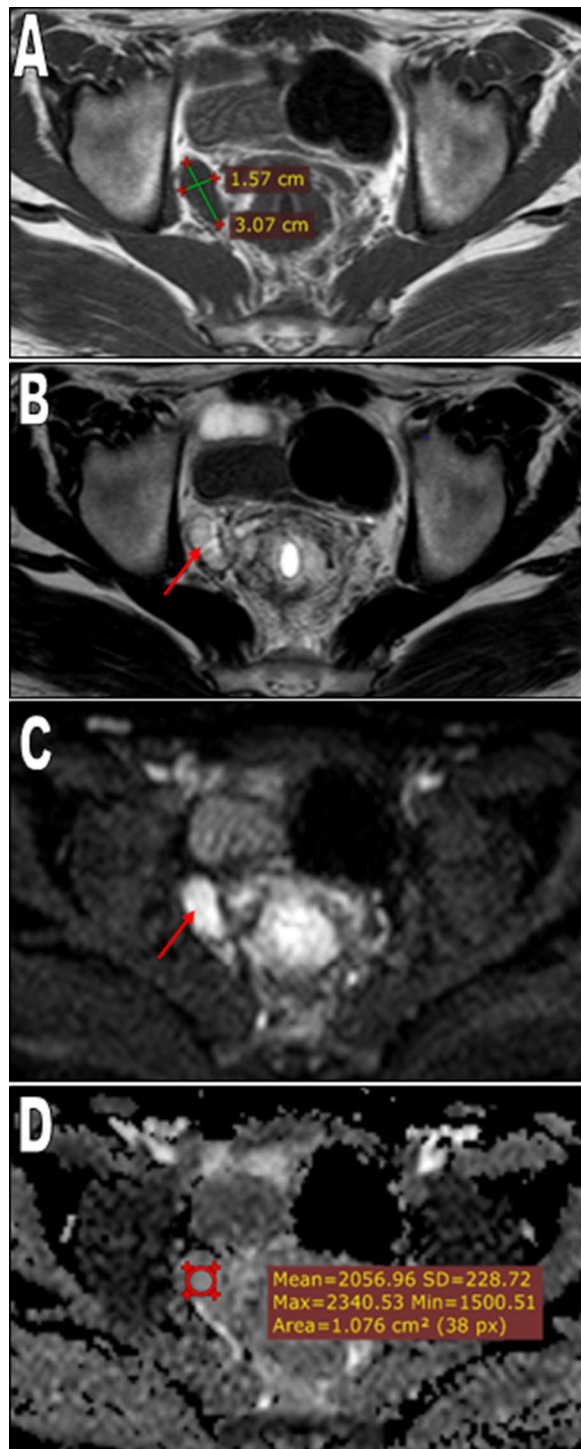
- **Functional assessment** shows accuracy of 50% and sensitivity of 26.90%.
- **Morphological assessment** shows accuracy of 72.69% sensitivity of 57.69%.

Morphological criteria have a higher accuracy of 72.69% in detection of metastatic regional lymph nodes (compared to 50% for ADC value) with a higher sensitivity of 57.69% (compared to 26.9% for ADC value), specificity of 90.91% (compared to 77.3% for ADC value), PPV of 88.24% (compared to 85.33% for ADC value), and NPV of 64.52% (compared to 47.22% for ADC value).

Discussion

Colorectal cancer is of a high prevalence in more developed countries than less developed ones. However, mortality rates are reduced in more developed countries as a result of screening and advancements in the diagnosis, staging, and treatment of rectal cancer [7].

Cancer rectum is prone to systemic metastasis as well as local recurrence. Mortality rates of rectal cancer have been declining over the past few decades due to improved



◀ **Fig. 4** MRI for a 25-year-old male patient with pathologically proven rectal mucinous carcinoma presented clinically with bleeding per rectum. **A** Axial T1 WI and **B** Axial T2 WI showed enlarged right peri-rectal lymph node, measuring about 30 × 16 mm at maximum axial dimensions, eliciting low T1 and heterogeneous high T2 signals, has an oval configuration with regular borders, morphologically it is considered to be suspicious lymph node. **C** DWI and **D** ADC map showed no restricted diffusion; with the predominant bright areas on DWI corresponding to high signal areas on the ADC map. ADC mean = 2×10^{-3} mm²/s. Histopathological analysis confirmed metastatic nature of the examined lymph node

survival rates. Therefore, it is critical to accurately predict the need for neoadjuvant chemotherapy and radiation prior to surgery [8].

With multiple studies evaluating the viability of ADC in differentiating metastatic from non-metastatic nodes in primary rectal cancer, DWIs have lately emerged as an essential functional imaging technique for identifying nodal metastasis [8].

This study aimed to determine the effectiveness of functional imaging using MRI with DWI in detection and characterization of loco-regional lymph nodes in primary rectal cancer as well as precision of its ability to distinguish between metastatic and non-metastatic nodes.

We found that adding the DWI images and ADC map to conventional sequences of the MRI resulting in higher sensitivity in distinguishing metastatic and non-metastatic lymph nodes from rectal adenocarcinoma, however, there was no difference regarding the accuracy. As functional assessment using ADC values shows accuracy of 86.52% and sensitivity of 86.24%, morphological assessment using conventional MRI sequences yielded an accuracy of 86.52% and sensitivity of 27.27%.

Cho et al. [8], in consistence with our study, specified a cutoff value of 1.0×10^{-3} mm²/s with maximum accuracy of 72%, sensitivity of 78%, specificity of 67%, and PPV of 61% for separating metastatic from non-metastatic regional lymph nodes in rectal cancer.

Ge et al.'s [3] results agreed also with ours as they found that the mean ADC value for metastatic lymph nodes was $1.17 \pm 0.16 \times 10^{-3}$ mm²/s, which was likewise noticeably less than that of benign lymph nodes $1.29 \pm 0.15 \times 10^{-3}$ mm²/s.

Unlike Yu et al. [9], who claimed that metastatic lymph nodes were substantially more likely to have higher ADC values, they went on to clarify that their findings are likely due to the fact that metastatic lymph nodes are more heterogeneous than non-metastatic ones. Additionally, they noted that there might be more blood vessels and vascular alterations brought on by the tumor in the metastatic lymph nodes.

The reviewed literature like Kim et al. [10], Ge et al. [3] and Cho et al. [8] excluded non-adenocarcinoma

TNM staging system and therapy, including widespread use of MRI and enhanced radiologist awareness of the rectal cancer TNM staging features [7].

Nodal metastasis is regarded as one of the key prognostic markers for both local recurrence and disease-free

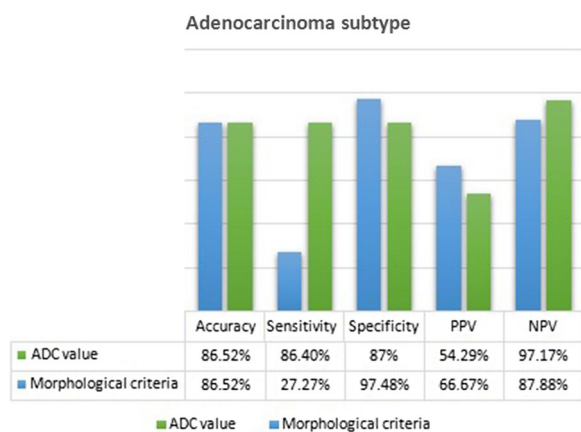


Fig. 5 Chart comparing ADC value versus morphological criteria for adenocarcinoma group

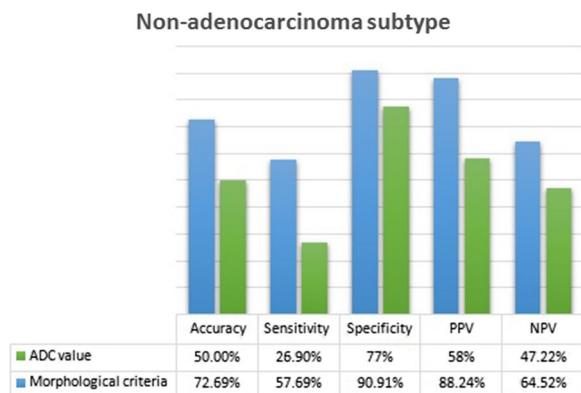


Fig. 6 Chart comparing ADC value versus morphological criteria for non-adenocarcinoma group

subtype from their studies because the mucin’s extremely high ADC value could bias the results. However, due to a reliable number of non-adenocarcinoma subtype in our study, they were examined as a separate category, and we found that we cannot discriminate non-metastatic and metastatic lymph nodes from non-adenocarcinoma subtypes based on ADC values owing to their extremely high mucin content that raise their ADC values significantly.

Furthermore, we found that morphological assessment using conventional sequences of the MRI has a better accuracy and sensitivity than DWI images and ADC map in distinguishing metastatic from non-metastatic lymph nodes in non-adenocarcinoma group (mucinous and signet ring cell). As morphological assessment yielded an accuracy of 72.69% and sensitivity of 57.69%, functional assessment shows accuracy of 50% and sensitivity of 26.90%. This could be explained by extremely high ADC

values of the lymph nodes of this group owing to their high mucin content.

Almlöv et al.’s [11] results were more or less comparable to ours as they found a maximum accuracy for discriminating metastatic and non-metastatic nodes according to MR morphological criteria of 91.3% with sensitivity of 35.3%, specificity of 97.0%, PPV of 54.6% and NPV of 94.0%.

Kono et al. [12] claimed that they found rectal cancer metastases in LN as a tiny as 1 mm in diameter, leading them to the conclusion that size criteria alone cannot reliably predict the LN involvement of rectal cancer.

Likewise, Borgheresi et al. [13] stated that combining morphological parameters with other advanced MRI techniques or functional parameters as DWIs will improve the diagnostic performance.

This study found that ADC value and MRI morphological criteria have a comparable accuracy in detection of metastatic regional nodal spread with the ADC value that has a better sensitivity in rectal adenocarcinoma, while morphological assessment has a higher accuracy, sensitivity and specificity in nodal spread detection for non-adenocarcinoma group. This could be explained as mucinous and signet ring cell rectal tumors has a high mucin content, which increase their ADC values making it of low diagnostic value in assessing metastatic nodal spread.

We acknowledge some limitations that should be mentioned. Tiny lymph nodes smaller than 2 mm were excluded because it was difficult to manually place the ROI in the center of the lymph node, which could have led to imperfect match with the histopathological data. Mismatches may have happened when multiple lymph nodes were detected on MRI. As long as all of the collected LNs were either metastatic or not, there was no issue with the radiologic–pathologic matching. Although we made every attempt to track LNs, complete matching was not possible in the situation of mixed LNs nature.

Conclusions

In conclusion, MRI functional imaging using ADC values could be used to distinguish metastatic and non-metastatic lymph nodes in rectal adenocarcinoma with a diagnostic accuracy of 86.52%. However, morphological assessment using conventional MRI was found to be better in assessment of regional lymph nodes at mucinous and signet ring rectal carcinoma.

Abbreviations

- ADC Apparent diffusion coefficient
- CRT Neoadjuvant chemoradiotherapy
- DWIs Diffusion-weighted imaging
- FOV Field of view
- LARC Locally advanced rectal cancer

LN	Lymph nodes
MRI	Magnetic resonance imaging
ROI	Region of interest
TE	Echo time
TR	Repetition time

Acknowledgements

Not applicable.

Author contribution

MFA, AAH, SMMG, RMMA, MEMS, and SHI contributed equally to this work. MFA, AAH, SMMG, and SHI designed the research. MFA, AAH, RMMA, and SMMG performed the research. MFA, AAH, SMMG, MEMS, and SHI analyzed the data. MFA, AAH, SMMG, and SHI wrote the paper. All authors have read and approved the manuscript.

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Availability of data and materials

All the datasets used and analyzed during this study are available with the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the research ethics committee of the Radiology department of the Faculty of medicine Cairo University on 28/2/2021, reference number (MD-8-2021). All patients included in this study gave a written informed consent to participate in the research. If the patient was less than 16 years old, or unconscious at the time of study, written informed consent was given by their parent or legal guardian.

Consent for publication

All patients included in this study gave a written informed consent to publish the data contained in this study. If the patient was less than 16 years old, or unconscious at the time of study, written informed consent was given by their parent or legal guardian.

Competing interests

The authors declare that they have no competing interests.

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