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Diagnostic performance of minimum and mean apparent diffusion coefficient parameters in evaluation of resectable rectal cancer

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ABSTRACT

Objective: To investigate the diagnostic correlations between MinADC and MeanADC values of resectable rectal cancer with tumoral histopathological features.
Methods: This cross-sectional study included 52 rectal cancer patients that were subjected to preoperative MRI and DWI. MeanADC and MinADC values were calculated and correlated with clinicopathological characteristics.
Results: MeanADC and MinADC values correlated statistically significant with tumor histological grade (MeanADC: t= 2.494, p = 0.016; MinADC: t = 2.857, p = 0.006). MeanADC correlated significantly with T-classification (MeanADC: t = 2.678, p = 0.010) and with perineural invasion(MeanADC: t = 2.525, p = 0.015). MeanADC and MinADC statistically correlated significantly with extramural vascular invasion (MeanADC: t = 2.023, p = 0.048; MinADC: t = 2.055, p = 0.045) and CRM invasion MinADC showed statistically significant correlation(MinADC: t=2.657, p=0.011). MinADC values showed higher diagnostic efficacy in discriminating well vs poor and moderately differentiated rectal cancer than MeanADC values, with threshold value of $0.55x10^{-3}mm^2/s$ (sensitivity, 58%; specificity, 90%)but MeanADC values showed higher diagnostic efficacy in discriminating extramural vascular invasion than MinADC values with threshold value of $1.21x10^{-3}mm^2/s$(-sensitivity, 77.8%; specificity, 76.7%).
Conclusion: Pretreatment combination of mean and minimum ADC values used as a non-invasive parameter to evaluate the aggressiveness of rectal cancer.

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KEY WORDS
Diffusion weighted imaging; Minimum ADC; Mean ADC; Rectal cancer.

Introduction

Rectal cancer is a major cause of cancer-related death[1]. In recent years, colorectal cancer has become the 4th most deadly cancer with about 900,000 deaths annually in the world, while rectal cancer alone accounts for 30%-35% of these cases[2] . The patients benefit in overall survival from early diagnosis[3].The rectal cancer prognosis depends on tumor invasion through the bowel wall, mesorectal fascia involvement, lymph node metastasis, vascular wall invasion and histology type[4]. The poor prognostic factors such as poor differentiation, high degree of TNM stage, extramural venous invasion (EMVI), and perineural invasion (PNI) affect the choice of therapies, especially for adjuvant radiation and chemotherapy protocols [5].

According to National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline, patients with T1N0M0 stage are treated by endoscopic surgery while advanced stages receive treatment as chemotherapy, radiotherapy and surgical resection[6].

Magnetic resonance imaging (MRI) plays a great role in rectal cancer risk stratification[7]. MRI techniques can identify, quantify and assess different cancer biomarkers [8].

Diffusion-weighted imaging (DWI) as a noninvasive MRI technique helps in assessment the Brownian movement of water molecules reflecting the biological features of a tissue by apparent diffusion coefficient (ADC) values [2]. DWI detects malignant tissue in different organs and is helpful in the preoperative diagnosis and decision of treatment [9].

The decrease in ADC values in high-grade tumors is due to increased cellularity with decreased extracellular space restricting water movement [10]. ADC is a useful imaging biomarker in the diagnosis, differentiation and predicting tumor response [11].

However, due to the effects of methods of region of interest (ROI) measurement and b-value selection on ADC value, different results about ADC have been reported to predict tumor's grade. Also, most studies had small numbers of cases and just focused on the MeanADC value only not including the MinADC value [11].

Combination of MinADC and MeanADC values helps in accurate grading of many tumors [12].

Some studies showed that MinADC values were more likely to reflect the density of tumor cells than the MeanADC values, so it was described as a marker to identify specific tumor biological features and predict tumor behavior [13].

Patients And Methods

Patients

This cross-sectional study was approved by the institutional review board of our hospital. 52 patients with pathologic diagnosis of rectal cancer by biopsy received preoperative MRI examinations, including DWI and ADC maps were enrolled through 2 years.

Inclusion criteria: 1) proven cases of rectal carcinoma, 2) surgical resection without therapy, 3) availability of pathological reports 4) evaluation via MRI with DWI and ADC maps.

Exclusion criteria: 1) long interval between MRI and surgery >1 month 2) no identified tumor signal on DWI and ADC map

Ethical consideration: The study was approved by Faculty of Medicine Research Ethics Committee which is organized and operated according to guidelines of International Council on Harmonization (ICH), the Islamic organization for Medical Science (IOMS), The united States Office for Human Research Protections and United Sates Code of Federal Regulations and Operates under Federal Wide Assurance No. FWA 000017585 obtained on 23/8/2021; also informed consent was obtained from all patients included in the study.

MR Imaging

The patient relaxed in flat position with the coil being around the pelvis. The MR images were performed

Table 1: Correlations between MeanADC, MinADC with clinicopathologic characteristics

Parameters	Number	MeanADC ($x10^{-3}mm^2/sec$)	P-value	MinADC ($x10^{-3}mm^2/sec$)	P-value
Gender			0.974		0.540
Male	21	1.31±0.43		0.55±0.29	
Female	31	1.31±0.23		0.50±0.28	
Location			0.728		0.805
Lower	19	1.32±0.41		0.55±0.25	
Mid-lower	4	1.51±0.41		0.61±0.59	
Middle	5	1.22±0.1		0.6±0.23	
Mid-upper	9	1.3 ± 0.24		0.48±0.3	
Upper	15	1.29±0.25		0.47±0.23	
T classification			**0.010**		0.212
T1-T2	29	1.41±0.23		0.56±0.29	
T3-T4	23	1.19±0.37		0.47±0.27	
N classification			0.570		0.427
N0	42	1.35±0.28		0.53±0.3	
N1-N2	10	1.14±0.43		0.47±0.21	
Differentiation grade			**0.016**		**0.006**
Well	4	1.68±0.26		0.88±0.34	
Moderate-poor	48	1.28±0.31		0.49±0.26	
PNI			**0.015**		0.824
Negative	45	1.35±0.27		0.52±0.3	
Positive	7	1.04±0.49		0.5±0.17	
EMVI			**0.048**		**0.045**

Negative	43	1.35±0.33		0.56±0.29	
Positive	9	1.12±0.16		0.35±0.19	
CRM invasion			0.275		**0.011**
Negative	44	1.33±0.34		0.56±0.28	
Positive	8	1.2±0.16		0.29±0.19	

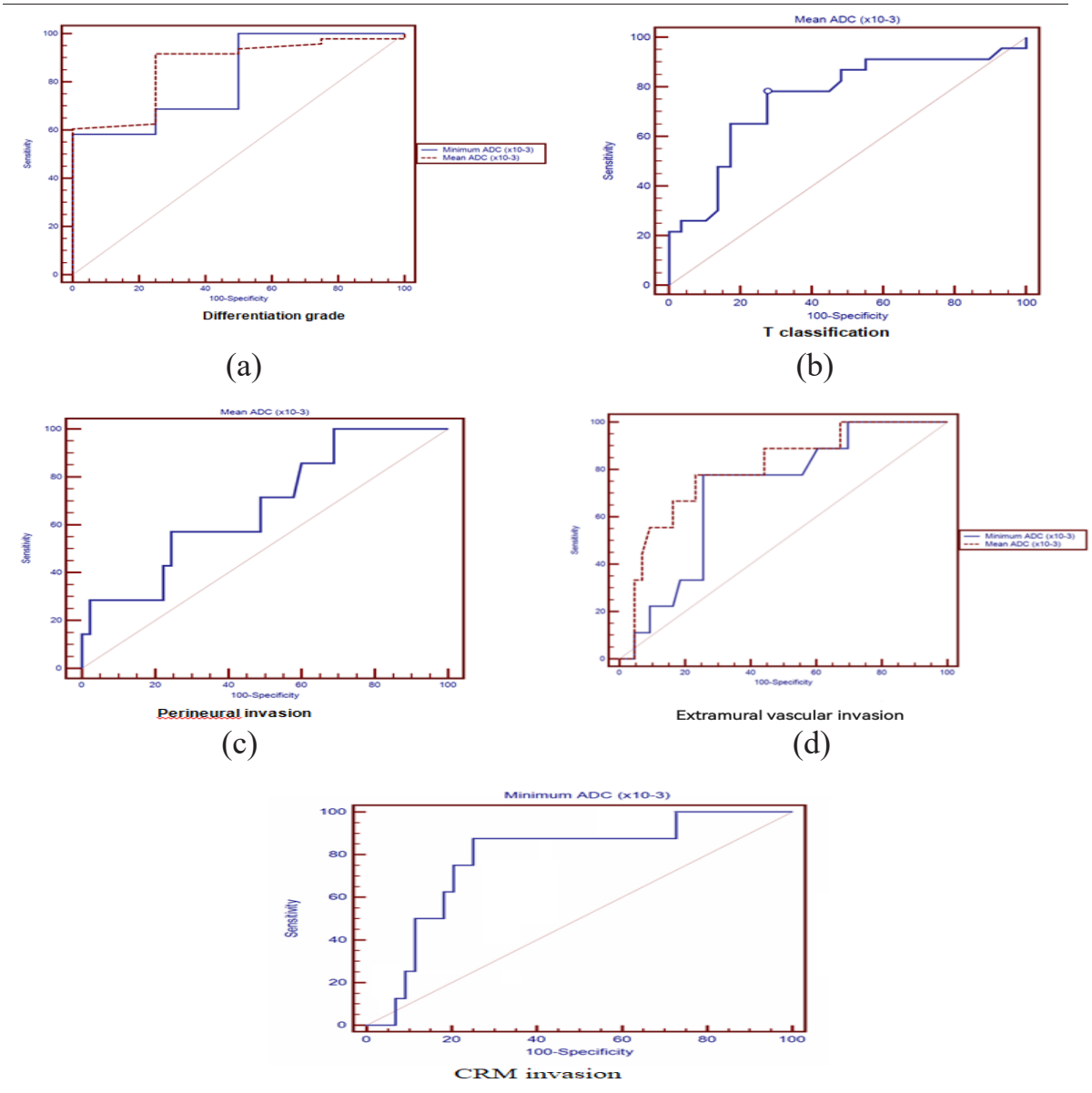


Fig. 1: ROC curve analysis of: (a) MinADC and MeanADC for discrimination of well vs moderately-poorly differentiated, (b) MeanADC for discrimination T1-2 vs T3-4, (c) MeanADC for discrimination of negative vs positive PNI, (d) minimum and mean ADC in discrimination of negative vs positive EMVI, (e) MinADC in discrimination of CRM invasion.

Table 2: ROC analysis for diagnostic performance of MeanADC and MinADC with rectal cancer characteristics

Parameters	Cut off point ($x10^{-3}mm^2/s$)	AUC	Sensitivity (%)	Specificity (%)	PPV	NPV
T classification						
T1-T2 vs T3-T4						
MeanADC	≤1.3	0.755	78.3	72.4	69.2	80.8
Differentiation grade						
Well vs low-moderate						
MinADC	≤0.55	0.855	58.3	90.0	100.0	16.7
MeanADC	≤1.58	0.818	91.7	75.0	97.8	42.9
PNI						
Negative vs Positive						
MeanADC	≤1.16	0.678	57.14	75.56	26.7	91.9
EMVI						
Negative vs Positive						
MinADC	≤0.38	0.709	77.8	74.4	38.9	94.1
MeanADC	≤1.21	0.800	77.8	76.7	41.2	94.3
CRM invasion						
Negative vs Positive						
MinADC	≤0.38	0.781	87.5	75.0	38.9	97.1

using Philips Ingenia (1.5Tesla). The sequences included the axial T1WI, sagittal, coronal and oblique axial (field of view: 28cmx28cm, 10cmx16cm, respectively) T2WI, axial fat suppressed T2WI and axial DWI. DWI images were obtained using the b values of 0, 600, and 800 s/ mm^2.

ADC Evaluation

ADC maps were generated from DWI with b value of 800 s/mm^2. The ROI for the solid tumor was manually determined on all tumor slices at the workstation. The values have been calculated automatically. Both MeanADC and MinADC values were acquired from the whole tumor ROI and the MinADC value was calculated automatically. The necrotic and haemorrhagic regions were avoided.

Potential prognostic histologic Factors

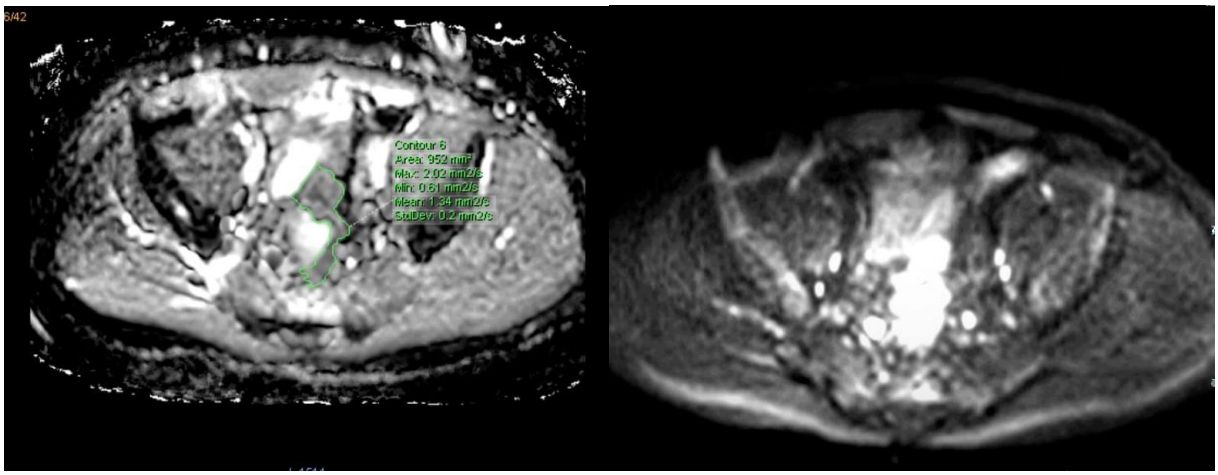
Pathologic reports were revised to determine the tumor T, N stage, differentiation grade, EMVI, PNI, and CRM invasion. Pathological TNM stage was determined regarding the 8^{th} edition of the American Joint Committee on Cancer tumor-node-metastasis staging system.

Statistical analysis

Data were revised and coded to the Statistical Package for Social Science version 23. The comparison

CASES:

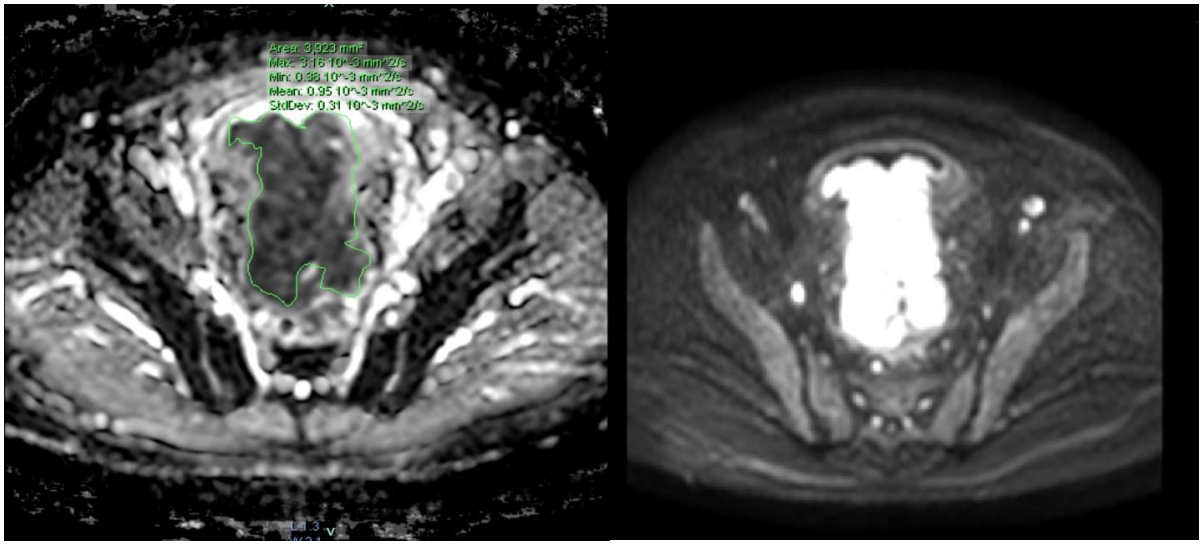
Case one



(a) **(b)**

Fig. 2: *A 44-year-old patient recently diagnosed with upper rectal cancer underwent MRI examination before surgery, (a)ADC, (b)DWI. MeanADC=1.34x10^{-3}mm^2/s, MinADC=0.61x10^{-3}mm^2/s. The patient's pathology report showed that his case was well differentiated adenocarcinoma staged as T2N0 with negative PNI, EMVI and CRM invasion.*

Case two



(a) **(b)**

Fig. 3: *A 59-year-old patient recently diagnosed with upper rectal cancer underwent MRI examination before surgery, (a)ADC, (b)DWI. MeanADC=0.95x10^{-3}mm^2/s, MinADC=0.38x10^{-3}mm^2/s. The patient's pathology report showed that his case was poorly differentiated adenocarcinoma staged as T4N2 with positive PNI, EMVI and CRM invasion.*

between groups regarding qualitative data was done by using ***Chi-square test*** and/or ***Fisher exact test***. The comparison between two independent groups with quantitative data and parametric distribution was done by using ***Independent t-test.*** The comparison between > 2 independent groups with quantitative data and parametric distribution were done by using ***One Way ANOVA test.***

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P-value > 0.05: Non-significant (NS), < 0.05: Significant (S), < 0.01: Highly significant (HS).

Results

MRI Findings

Rectal cancer appeared as an asymmetrical increased circumferential wall thickening narrowing the lumen and mounting to mass formation. It was isointense or hypointense on T1WI and hyperintense on T2WI with hyperintensity on DWI and hypointense on ADC map.

Clinical and histopathological findings

We have examined 52 pathologically proven rectal cancer patients, 31 female (59.6%) and 21 male (40.4%). The mean age was 49.19 years old ranging from 21 to 69 years old. Regarding cancer location, 19 cases were at lower rectum (36.5%), 4 cases were at mid and lower rectum (7.7%), 5 cases were at middle rectum (9.6%), 9 cases were at middle and upper rectum (17.3%) and 15 cases were at the upper rectum (28.8%). The values of MinADC of the examined cases ranged from 0.04 to $1.27x10^{-3}$ mm^2/s while MeanADC ranged from 0.9 to $2.3x10^{-3}$ mm^2/s.

Regarding the histopathological characters: T classification: 29 cases were categorized as T1-T2 (55.8%) while the remaining 23 cases were classified as T3-T4 (44.2%), regarding N classification, 42 patients had no lymph node metastases N0 (80.8%) while 10 patients categorized as N1-N2 (19.2%). Regarding the tumor differentiation, 44 cases were moderately differentiated adenocarcinoma (84.6%) while 4 cases were well differentiated and 4 cases were poorly differentiated by a percentage of (7.7%) for each differentiation grade. PNI was detected in only 7 cases (13.5%) while 45 cases showed no PNI (86.5%). EMVI was present in 9 patients (17.3%) and absent in 43 patients (82.7%). Finally, CRM invasion were seen in only 8 patients (15.4%) while 44 patients showed free CRM (84.6%) (Table 1).

Associations between MeanADC, MinADC values with clinicopathological Features

We have found that there was no significant correlation between minimum and mean ADC values with the age, sex of patients and with tumor location.

We have found that as minimum and mean ADC values decreased, the more the aggressiveness of the tumor (poorly to moderately differentiated, stage T3-T4, stage N1-N2, positive EMVI, PNI and CRM invasion) while as the minimum and mean ADC values increased, the less the aggressiveness of the tumor with different statistically significant correlation.

The lower the degree of the differentiation, the lower the mean and minimum ADC; MinADC: t=2.857, p=0.006 (highly significant); MeanADC: t=2.494, p=0.016 (significant).

The advanced T stage (T3/ T4) showed lower mean and minimum ADC. Only MeanADC was significantly lower for tumors with higher T stage; MeanADC: t=2.678, p=010 (significant). Although the T stage increased as the MinADC decreased, there was no statistically significant correlation in-between.

The lower the minimum and mean ADC, the higher the N stage, both MeanADC and MinADC did not differ significantly; MeanADC: t=0.573, p=0.570, MinADC: t=0.802, p=0.427.

The patients with positive PNI had MeanADC: t=2.525, p=0.015(significant); MinADC: t=0,224, p= 0.824 (non-statistically significant). As regard the EMVI both mean and minimum ADC values were statistically significant with presence of EMVI; MeanADC: t = 2.023, p=0.048 (significant); MinADC: t=2.055, p=0.045).

While the CRM invasion was significantly correlated with MinADC only t=2.657, p=0.011 but there was not statistically significance between CRM invasion and MeanADC.

ROC analysis

ROC curve analysis (Table 2, Fig 1) indicated that

MinADC was identified to have higher diagnostic efficacy in differentiating well vs moderately-poorly differentiated rectal cancer than the MeanADC. The sensitivity of MinADC with a cut off $0.55x10^{-3}mm^2/s$ as the threshold for well differentiated rectal cancer was 58%, and the specificity was 90% with a higher AUC (0.855). The sensitivity of MeanADC with a cut off $1.58x10^{-3}$ mm^2/s as the threshold for diagnosis of well differentiated rectal cancer was 91.7%, and the specificity was 75%. These results showed importance of the MinADC in discriminating the differentiation of rectal cancer.

The MeanADC was identified to have higher diagnostic efficacy in detection the presence of EMVI than the MinADC. The sensitivity of MeanADC with a cut off $1.21x10^{-3}$ mm^2/s as the threshold for positive EMVI was 77.8%, and the specificity was 76.7 % with a higher AUC (0.800). The sensitivity of MinADC with a cut off $0.38x10^{-3}$ mm^2/s as the threshold for detection of EMVI was 77.8%, and the specificity was 74.4% with AUC (0.709).

The MeanADC was identified to have high diagnostic efficacy in differentiating T1-T2 from T3-T4 and presence of PNI with sensitivity and specificity of 78.3 and 72.4 % respectively and a cut off $1.3x10^{-3}$ mm^2/s with an AUC (0.755) as regard the T stage and sensitivity and specificity of 57.14 and 75.56 % respectively and a cut off $1.16x10^{-3}$ mm^2/s with an AUC (0.678) as regard the presence of PNI.

Only MinADC showed high diagnostic efficacy in differentiating positive and negative CRM invasion with sensitivity and specificity of 87.5 and 75% respectively and a cut off $0.38x10^{-3}$ mm^2/s with an AUC (0.781).

Discussion

The value of ADC in clinical practice is still controversial [14]. Many studies have reported that new MRI techniques can determine morphological and functional parameters that can be associated with measurements of tumor biology[15].

Most of these studies used the MeanADC value for correlation with the tumor biological features, yet MinADC values could reflect the most malignant parts of tumors better than MeanADC values[16].

In our study we measured both mean and minimum ADC to assess its diagnostic performance in evaluation of resectable rectal cancer.

ADC values are powerful prognostic indicator in assessment and treatment of rectal cancer. ADC levels might reflect the aggressiveness of the tumor tissue[7].

In this study we have found that both minimum and mean ADC decreased when the aggressiveness of the tumor increased (poorly to moderately differentiated, stage T3-4, stage N2, positive EMVI, PNI and CRM invasion) as many other studies [7,15,17].

In our study, regarding the tumor differentiation grade, we found that there was statistically significant correlation between both MeanADC and MinADC with tumor grade. These results were consistent with results of Akashi et al. [18] who found that there was statistically significant correlation between MeanADC and tumor grade. Also, our results were similar to Liu et al who found that there was statistically significant correlation between both mean and MinADC with the differentiation grade and suggested that MinADC being more significant in detection well differentiated cases vs moderately /poor differentiated cases and that were compatible with our results with some differences in the sensitivity being 58%, 91% for minimum and mean ADC respectively compared to 80% for both in their study. Curvo-Semedo et al.[16] evaluated a statistically significant correlation between MeanADC and the differentiation grade (p=0.025). In contrast, Surov et al.[7] ,Sun et al.[8] , Ma et al. [14], Kargol et al.[15], Tang et al.[19] and Yuan et al.[19] showed that there was no significant correlation between measured ADC and tumor grade in their studies. This disagreement may be due to the method of measuring of the ADC values in different research as the used ROI in our research and in Liu et al. [2] assessed the whole tumor volume not only single slice ROI reflecting the largest size of the tumor.

A study from Lambregts et al.[20] demonstrated that ADC values obtained from the whole tumor volume provide the most reproducible results. Based on the observations from their study, the small sample ROI may have resulted in lower ADC values, which can be caused by the inclusion of only the most viable solid parts of the tumor, skipping the regions of necrosis[15].

Also, Akashi et al.[18] reported that some patients with well differentiated adenocarcinoma had lower ADC when compared with ADC value of others with

the same differentiation grade. These lower ADC cases had more fibroblasts and lymphocytes in the interstitial space of the tumor than others. Several studies reported that tissue fibrosis is associated with lower ADC values in patients with other cancers. So, the more cases of marked interstitial fibrosis the lower ADC values will be measured even if these case of well differentiated type[21,22].

Regarding T stage of the tumor, in this study, there was significant difference between the ADC value and pathological T staging of rectal cancer; negative correlations were observed between preoperative ADC and T staging of the tumor. As the T stage increased, lower ADC were detected. So in this study we found the MeanADC was able to differentiate T1-T2 group from T3-T4 group with a cut off value of $1.3x10^{-3}$ mm^2/sec, this is with agreement with Liu et al.[2] , Sun et al.[8] Kargol et al.[15], Akashi et al.[18] and Ao et al.[23] who all concluded that MeanADC were statistically significant with T stage.

In our study we demonstrated that MinADC decreased with high tumor T stages (T3-T4), but this difference was of no statistically significant correlation and that is in contrast to Liu et al [2] who stated that MinADC were statistically significant with T stage of the rectal tumors.

Many studies tested only MeanADC without measuring MinADC and found that there was also no statistically significant correlation between measured MeanADC and T stage of the tumor as Surov et al.[7], Curvo semedo et al.[16], Tang et al.[17] and Yuan et al.[19] and so their results were not in agreement with our results.

Regarding N stage of the tumor, In our study, the more the decrease measured mean and minimum ADC, the more the advanced N stage however this trend was not statistically significant also. Sun et al.[8] , Tang et al.[17], Akashi et al [18], Yuan et al.[19] and Ao et al.[23] agreed with us with no statistically significance between measured MeanADC and N stage of the tumor, in addition to Yuan et al[19] who tested also MinADC and agreed with our results.

Opposite to our results, Liu et al.[2] and Li et al.[4] proved that there was statistically significant correlation between measured mean and minimum ADC with N stage of the tumor, also Kargol et al.[15] and Curvo-Semedo et al.[16] stated that there was statistically significant correlation between only MeanADC and N stage.

Akashi et al.[18] analyzed that inconsistency through that the nodal status were analyzed with thin sectioned histologic planes. These histologic analyses enabled detection of micro metastases in small lymph nodes and were not detected with MRI.[18]

The reason for these varying results may be due to the differences between preoperative and postoperative TN stages or due to the small number of cases. Also, ADC value may also be affected by the person who performed the ADC measurement, because there is no standardized method for ADC measurement at present and it is affected by ROI and used b-value[4].

In our research, MeanADC was different significantly for patients with present PNI vs absent invasion (P=0.015), with a cut off value of $1.16x10^{-3}mm^2$/sec and 57%,75% sensitivity and specificity respectively, this agreed with Liu et al.[2] who showed statistically significant difference between MeanADC and positive PNI cases with 67% and 60% sensitivity and specificity respectively, while the MinADC in our study showed no statistically significant correlation with the presence of PNI unlike the results of Liu et al.[2] who proved statistically significance between MinADC and PNI positive cases. Unlike our results Sun et al.[8] found that there was no significant correlation between MeanADC and PNI.

Regarding the EMVI, our study showed there was significant correlation between both mean and minimum ADC and EMVI with 77% sensitivity for both with a cut off value of $1.21x10^{-3}mm^2/s$ and $0.38x10^{-3}mm^2/s$ respectively, this was in line with Liu et al.[2] with lower sensitivity being 21.6% for mean ADC and 51.7% for MinADC in their study. Ao et al.[24] agreed with our findings regarding MeanADC. Opposite to our results, Sun et al.[8], Kargol et al.[15] , Curvo-Semedo et al.[16], Akashi et al.[18] and Yuan et al.[19] suggested that there was no statistically significance between MeanADC and PNI. A study by Li et al.[4] showed no statistically significant correlation between both minimum and MeanADC and presence of EMVI and that is also opposite to our results.

In our study, there was statistically significant correlation between MinADC and CRM invasion while there was no statistically significant correlation between MeanADC and CRM invasion, The results of Sun et al.[8] found that MeanADC didn't have statistically significant correlation with CRM invasion as our results but opposite to our results, Kargol et al.[15], Curvo-Semedo et al.[16] , Akashi et al.[18] and Tong et al.[25] stated that there was statistically significance between MeanADC and CRM invasion. We could not find any research agreed with our results as the significance of MinADC in detecting the presence of CRM invasion as most of the research used only MeanADC without using MinADC in rectal cancer.

Limitations

First it was a single-center study on a relatively small group of patients affecting the statistical power but that was caused by most of the rectal cancer cases were discovered in late stages where the tumor was irresectable and those patients received treatment so they were excluded from our study. Second, our ADC measurements were achieved by evaluating whole tumor ROI and that was time consuming and difficult to perform in clinical practice. Third, evaluation of MRI examination is observer-dependent with certain measurement error would appear for ROI selection and its size effects. Fourth, although we used T2WI to prevent contamination of cystic and/or necrotic components, minor contamination might not be avoided owing to the large slice thickness of T2WI. Fifth, the ADC was calculated from only one b-value. Our study was a retrospective design so limited data availability and may be prone to selection bias.

Conclusion

Pretreatment combination of mean and minimum ADC values used as a non-invasive parameter to evaluate the aggressiveness of rectal cancer. **R**

Abbreviations: EMVI: extramural vascular invasion, DWI: Diffusion- weighted imaging, MRI: magnetic resonance imaging, PNI: perineural invasion, CRM: circumferential resection margin, ADC: apparent diffusion coefficient, T1-weighted images: T1WI, T2-weighted images: T2WI, MinADC: minimum ADC, MeanADC: mean ADC, FOV: field of view, PACS: picture archiving and communication system, ROC: Receiver operating characteristic curve, ROI: region of interest, AUC: area under curve , NCCN: National Comprehensive Cancer Network.

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