The value of apparent diffusion coefficient in predicting treatment response of rectal cancer after neoadjuvant radiation therapy

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Summary

Objective: To evaluate the value of the apparent diffusion coefficient (ADC) in predicting treatment response in rectal cancer patients after neoadjuvant chemoradiation therapy (nRCT). *Subject and method:* A study was conducted on 29 rectal cancer patients who underwent nRCT. Patients underwent magnetic resonance imaging (MRI), and tumor volume and ADC values (b-values: 0-1000s/mm^2) were measured before and after nRCT. ADC values were measured in two ways: 1. For the entire tumor (ADC_1) and 2. On the slice with the largest tumor area (ADC_2). Changes in tumor volume (ΔV) and ADC values (ΔADC) before and after treatment were compared with the surgical pathology results, categorized into complete response (pCR)/incomplete response and downstaging T/not downstaging T groups. *Result:* ΔADC values were higher in the downstaging T group compared to the non-downstaging T group, with ΔADC_1 values of 45.4% and 19.1%, respectively (p = 0.005), and ΔADC_2 values of 51.7% and 20.2%, respectively (p = 0.01). At the ΔADC_1 threshold of 42.2%, sensitivity was 55.6%, and specificity was 100%, while for ΔADC_2 at 18.1%, sensitivity and specificity were 88.9% and 72.7%, respectively. There was no statistically significant difference in ΔADC values between the complete response and incomplete response groups (p>0.05). Changes in tumor volume did not provide prognostic value for treatment response to NRCT. *Conclusion:* The ΔADC value is a potential prognostic factor in predicting treatment response in rectal cancer patients after nRCT, with more accurate diagnostic information compared to tumor volume.

Keywords: Rectal cancer, neoadjuvant radiation therapy, apparent diffusion coefficient.

1. Background

Rectal cancer (RC) is a common type of cancer in Vietnam and worldwide. According to Global cancer, in 2020, there were 732,210 new RC cases globally, accounting for 3.8% of all cancer cases. In Vietnam, the incidence rate of colorectal cancer is 14.1 per 100,000 population, there were no separate figures for colorectal cancer and rectal cancer [1]. The treatment strategy involving neoadjuvant chemoradiation therapy (nRCT) combined with total mesorectal excision (TME) has significantly reduced the risk of local recurrence, improving the 5-year survival rate to 65.2%, with a local recurrence rate within 5 years of 2.8%, and a 5-year survival rate of 86%. To tailor the treatment plan to each patient, accurate and timely assessment and response to nRCT treatment is essential. Currently, treatment response is primarily monitored by evaluating tumor size using computed tomography (CT) and magnetic resonance imaging (MRI). However, size-based assessments often lack the precision to distinguish response/non-response because of limited detection capability for residual small tumors,

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resulting in low negative predictive values [2]. FDG PET/CT has demonstrated some capabilities in assessing tumor response after neoadjuvant therapy; however, radiation-induced inflammation can lead to increased FDG uptake, reducing the ability to detect treatment response in the lesion.

Diffusion-weighted imaging (DWI) is a technique that has been employed to assess the treatment response of tumors in various types of cancer. It provides functional information about the microstructural characteristics of tumors by evaluating differences in the mobility of water protons, influenced by cell density, blood vessels, extracellular fluid viscosity, and cell membrane integrity. This information can be quantified through the measurement of the apparent diffusion coefficient (ADC). DWI is a non-invasive method that does not require contrast agents and does not involve ionizing radiation, unlike 18-FDG PET/CT. Some recent studies in our country have applied multi-parametric DWI in patients with rectal cancer both before and after neoadjuvant chemoradioation therapy (nCRT). However, most authors have only used qualitative diffusion-weighted imaging. In this study, we utilized quantitative measurements of the apparent diffusion coefficient (ADC) before and after treatment to predict the response to nCRT in patients with rectal cancer.

2. Subject and method

2.1. Study design

Neoadjuvant chemoradiotion therapy (nRCT) was administered to 29 patients diagnosed with rectal cancer at 108 Military Central Hospital from May 2022 to June 2023.

2.1.1. Patient selection criteria

Patients with a confirmed diagnosis of rectal cancer through pathological examination.

Patients who underwent nRCT following the guidelines of the National Comprehensive Cancer Network (stage II or stage III) and had pre-nRCT and pre-operative rectal MRI.

Patients who underwent rectal resection surgery after nRCT and had post-surgical pathological results.

2.1.2. Sample size: All eligible patients were included in the study.

2.2. Method

The study was conducted as a descriptive and prospective combined investigation.

Data analysis: Data were collected and analyzed using SPSS 22.0 software. Shapiro-Wilk tests were used to assess the normality of ADC_1, ADC_2, ΔADC_2, V, and ΔV values. Since the data did not follow a normal distribution, the Mann-Whitney U test was used to evaluate differences between the two groups. ΔADC_1 values were normally distributed, so an independent t-test was employed to assess the mean values in the two groups.

2.3. Protocols in the study

Patients were scanned using a 1.5T MRI machine from Philips following the protocol:

Sequences	TR/TE	FOV (cm)	Matrix	Slice thickness (mm)
T2W-TSE sagittal	6150/89	23	200 × 230	5
T2W-TSE axial and coronal	6800/67	20	200 × 200	5
DWI (b=1000 s/mm^2)	5500/68	26	200 × 260	5
T1-3D GRE (intravenous contrast)	3.66/1.36	25-30	240 × 300 (axial) 200 × 250 (coronal) 225 × 290 (sagittal)	3

ADC Values: ADC values were measured using the GE PACS system in two ways: 1. Measuring for the entire tumor and 2. Measuring on the slice with the largest tumor area. For method 1, a region of interest (ROI) was drawn along the edge of the high signal region on the b1000 image on each cross-sectional slice passing through the tumor. ADC values were calculated for each slice, and then the average was computed to obtain the mean ADC value for the entire tumor (referred to as ADC1). ROI was drawn only in the solid part of the tumor, guided by the b1000 and T2W images. For method 2, ROI was drawn similarly but only on the slice with the largest tumor area (referred to as ADC2). For tumors that no longer showed diffusion restriction on the b1000 image after treatment, ROI was placed based on the initial tumor location to calculate the ADC value after treatment. Δ ADC was calculated using the formula:

$$\Delta \text{ ADC (\%)} = ((ADC_{\text{post treatment}} - ADC_{\text{before treatment}}) / ADC_{\text{post treatment}}) \times 100\%$$

Tumor volume measurement: ROIs were drawn on T2W images, encompassing the entire tumor. The software calculated the tumor area for each slice (Si). The total tumor volume was calculated using the formula:

$$V = (\Sigma Si) \times (\text{slice thickness} + \text{interslice gap})$$

$$\Delta V = ((V_{\text{before treatment}} - V_{\text{post treatment}})/V_{\text{before treatment}}) \times 100\%$$

The post-surgical pathology results: Patients were considered to have achieved a complete response to treatment (pCR) when no tumor cells were found on histopathology, and instead, fibrotic and degenerative tissue was observed. In cases where tumor cells were still present, the extent of the tumor was reassessed based on the AJCC 8th edition criteria (pT). Downstaging occurred when the stage before treatment (clinical T-cT stage) was greater than the stage post treatment (pathologic T-pT stage).

3. Result

3.1. Characteristics of the study subjects

Table 1. Patients' characteristics (n = 29)

Characteristic			Value
Age ($\bar{X} \pm$ SD)			64.17 ± 10.78
Sex (%)	Male		58.6
	Female		41.4
cT before treatment (%)	T2		6.9
	T3		75.9
	T4		17.2
pT post treatment (%)	pCR		10.3
	pT	T1	20.7
		T2	27.6
		T3	37.9
		T4	3.4
pCR (%)			10.3
Downstaging T (%)			62.1

The average age of the study subjects was 64.17 ± 10.78 years, with 58.6% of the patients being male. Before treatment, the majority of patients were diagnosed at stage T3 (75.9%). After treatment, three patients (10.3%) achieved a complete response on histopathology. Patients with pT < 3 accounted for 58.6% of the group.

3.2. Apparent diffusion coefficient (ADC) values in predicting treatment response post NRCT

Table 2. Correlation between ADC values and treatment response (n = 29)

Characteristic		pCR		p*	T downstaging		p*
		Yes	No		Yes	No	
ADC_1	ADC_1	1.03	1.04	0.61*	1.04	1.06	0.62*
	ΔADC_1 (%)	33.8	35.6	0.91**	45.4	19.1	0.005**
ADC_2	ADC_2	1.06	1.01	0.83*	1.02	1.01	0.84*
	ΔADC_2 (%)	22.3	41.7	0.39*	51.7	20.2	0.01*

**Mann-Whitney U test, **Independent t – test.*

There were no statistically significant differences in ADC values before treatment and ΔADC values between the two groups: Complete response and no complete response, p>0.05.

ΔADC_1 and ΔADC_2 values showed statistically significant differences between the groups with and without downstaging T before and after treatment. Specifically, the group with downstaging T had a higher ΔADC value, with p<0.05.

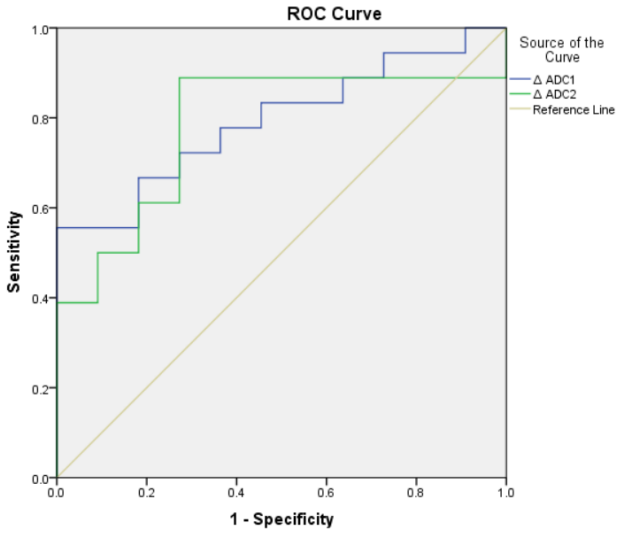

Figure 1. The ROC represents the relationship between ΔADC and downstaging T.

Table 3. The ROC parameters for the relationship between ADC and downstaging T

Parameter	AUC	Cut-off	Sensitivity	Specificity	Youden
ΔADC_1	0.793	42.2	55.6	100	0.556
ΔADC_2	0.783	18.1	88.9	72.7	0.616

The AUC was 0.793 for ΔADC_1 and 0.783 for ΔADC_2. At a threshold of ΔADC_1 = 42.2%, the sensitivity was 55.6%, and the specificity was 100%. For ΔADC_2 = 18.1%, the sensitivity and specificity were 88.9% and 72.7%, respectively.

3.3. Tumor volume values in predicting treatment response post nRCT

Table 4. Correlation between tumor volume and treatment response after nRCT

Characteristic	pCR		p*	T downstaging		p*
	Yes	No		Yes	No	
$V_{before\ treatment}$ (mm^3)	10.19	14.79	0.47	14.4	14.2	0.62
Δ V (%)	82.47	40.06	0.053	53.5	29.6	0.15

**Mann-Whitney U test.*

Tumor volume before treatment, as well as ΔV values, did not have predictive value for the response of the tumor to adjuvant treatment, p>0.05.

4. Discussion

Neoadjuvant chemoradiation therapy (nRCT) plays a crucial role in not only limiting local recurrence, downstaging T, and thereby improving the likelihood of complete tumor resection (with negative surgical margins) but also reducing the risk of recurrence. According to the NCCN guidelines, nRCT is indicatied to stage II or stage III (T3-4N0 or any T N1-2). Predicting the response of the tumor to treatment is essential, allowing for personalized treatment plans for each patient, ultimately leading to better outcomes. The results of our study showed that ADC and tumor volume values before treatment were not related to the response of the tumor to nRCT. Amodeo et al (2018) conducted a meta-analysis based on seven studies regarding the ADC value before treatment and found no statistically significant difference between the complete response group and the incomplete response group to nRCT, p=0.33 [3]. This result is similar to our study. However, Lambrecht (2012), in a study of 20 rectal cancer patients, concluded that there was a correlation between the degree of complete response (pCR) and the ADC value before treatment, p=0.003 [2]. Differences in outcomes between various studies are likely due to changes in nRCT protocols over time, thus affecting treatment efficacy. In our study, nRCT protocols and the time between patients varied, with some patients following treatment while others experienced emergency surgery due to complications. This heterogeneity can result in discrepancies in outcomes. In Lambrecht's study (2012), the complete response group had lower ADC values (0.94 ± 0.12 vs. 1.19 ± 0.22) [2]. This can be explained by more extensive tumor necrosis leading to higher ADC values. Tumor necrosis is often associated with poor blood supply, anaerobic metabolism, and an acidic environment, which can lead to reduced responsiveness to radiotherapy. Conversely, high ADC values are sometimes associated with mucinous rectal cancer, a subtype of cancer with a worse prognosis. Currently, to predict tumor response, immune tissue markers such as CD31, CD2-40, and S-100 can be used.

The results of our study also show no significant difference in ΔADC values between the complete response and incomplete response groups, p>0.05. Lambrecht (2012) found a significant difference in ΔADC values between the complete and incomplete response groups, which were 88 ± 35% and 26 ± 19%, respectively, p = 0.001 [2]. Amodeo (2018) based on the results of six different studies calculated ΔADC values between the two groups to be 59.7% and 29.7%, p = 0.016 [3]. Iannicelli et al. (2016) studied 49 rectal cancer patients and found a difference in ΔADC values between the groups with and without response to treatment, with values of 0.493 × 10-3mm^2/s and 0.293 × 10-3mm^2/s, respectively, p = 0.01 [4]. The differences in results between our study and other authors may be due to the small proportion of patients who achieved complete response to nRCT in our study (only 3/29 patients, 10.3%). Therefore, comparing two groups with such a difference in sample size may lead to

unreliable results. The increase in ADC values after treatment can be explained by tumor necrosis, inflammation, and replacement of cancer tissue with fibrotic lesions, thus altering the original tumor structure and reducing diffusion restriction. According to Lambrecht, if the ADC value does not increase, it indicates a tumor with a dense microstructure, leading to a poor response to treatment [2]. We can also see that even in the incomplete response group, the ADC value after treatment increased, indicating that nRCT is effective but not sufficient to eliminate all cancer cells.

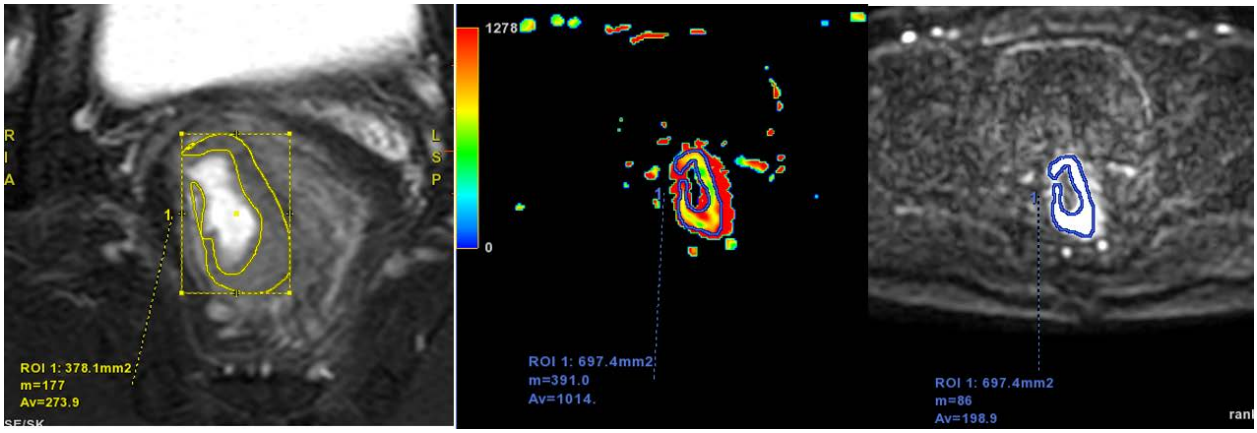

Figure 2. ROI drawing for calculating tumor volume and ADC Value on a Slice

Currently, comparing tumor volumes before and after treatment is often used to assess treatment response. According to our study, there was no significant difference in ΔV values between the complete response group and the incomplete response group ($p = 0.053$). According to Lambrecht (2012), the ΔV values between these two groups were 86 ± 12% and 60 ± 21%, respectively, with a statistically significant difference of $p=0.001$ [2]. The discrepancy in results could be attributed to the lower proportion of pCR patients in our study, accounting for only 10.3% (compared to 30% in Lambrecht's study), making group comparisons less precise.

The ΔV values showed no significant difference between the groups with or without downstaging T after nRCT, $p > 0.05$. Thus, tumor volume does not provide valuable prognostic information regarding treatment response. Palmisano et al. (2020) conducted a study on 43 rectal cancer patients, with 26% achieving complete response, 51% partial response, and 23% no response. The ΔV values for these groups were 86%, 75%, and 59%, respectively, with a statistically significant difference of $p = 0.005$ [5]. Conversely, according to Lambrecht (2012), there was no correlation between downstaging T and ΔV, with $p = 0.26$ [2], a result consistent with our study. Differences between studies may stem from difficulties in assessing the initial T stage (cT), which is subjective and can lead to discrepancies in grouping with or without downstaging T after treatment.

In our study, we assessed tumor volume after treatment when the tumor had regressed or necrotized. Measuring post-treatment tumor volume can be challenging due to difficulties in precisely determining the tumor's margin, as well as identifying residual tumor tissue. Both Palmisano and Lambrecht's studies indicated that ΔV early (around 10-15% of the expected nRCT duration) provided higher prognostic value compared to ΔV at the end of treatment [2, 5]. This is because determining the tumor's boundary at this stage is more accurate than after nRCT, making the ROI delineation more precise. Due to these limitations, Palmisano (2020) suggested using ΔV_{DWI} (measuring tumor volume on DWI) instead of $\Delta V_{T2\text{-}TSE}$ for improved accuracy [5].

ΔADC_1 and ΔADC_2 values were higher in the group with downstaging T compared to the group without downstaging T after nRCT, with a statistically significant difference of $p<0.05$. The AUC values were 0.793 and 0.783, respectively. At a threshold of ΔADC_1 = 42.2%, the sensitivity was 55.6%, and specificity was 100%. For ΔADC_2 = 18.1%, sensitivity and specificity were 88.9% and 72.7%, respectively. Joye et al. (2014) concluded that ΔADC values were valuable in predicting nRCT response in rectal cancer, with sensitivity and specificity of 80% and 78%, respectively [6]. According to Cerny (2019), the proportions of residual tumor tissue < 20% and fibrotic tissue > 70% were related to ΔADC values (10^{-6} mm^2/s), with p-values of 0.0015 and 0.0051, respectively [7]. Jacobs (2016) and Cai (2013) concluded that there was a difference in the ΔADC values between the good and poor response groups with nRCT at weeks 3-5 during the treatment process [8], [9]. Thus, ΔADC has prognostic value in assessing tumor response to treatment. Lambrecht (2012) suggested that ΔV had lower predictive value compared to ΔADC for complete response (pCR) or non-response to nRCT [2]. Both Lambrecht (2012) and Iannicelli (2016) concluded that ΔV before and after treatment did not have prognostic value in downstaging T [2]. These results are consistent with our study, highlighting that ΔADC is more valuable than ΔV in predicting tumor response. Currently, in addition to using the average ADC value as in our study, the development of 3D ADC mapping allows for the creation of ADC value charts, calculation of mean values, median values, 25^{th} and 75^{th} percentiles, and the interquartile range for more accurate comparisons before, during, and after treatment, improving the prognostic assessment of tumor response.

Furthermore, ROI delineation plays a crucial role in calculating ADC values. According to our study, in evaluating downstaging T, ADC values from both ROI delineation methods were valuable. Drawing the ROI encompassing the entire tumor provided better diagnostic value, with an AUC value of 0.793 compared to 0.783. According to Lambrecht (2011), there was no difference in ADC values between drawing the ROI around the entire tumor and drawing the ROI on a single slice [10]. However, delineating the entire tumor requires more time and may not be practical in clinical practice due to patient compliance, limited reading time, and other constraints. Drawing the ROI on the slice with the largest tumor area offers a balance between diagnostic value and practicality, making it more suitable for daily clinical practice.

Our study had several limitations, including a small sample size, evaluation only after treatment, and a lack of assessment during treatment. Changes in tumor characteristics due to treatment may vary over time, so determining the optimal timing for assessment is necessary to ensure accuracy. Additionally, current post-surgical pathology can classify tumor response to nRCT based on the Mandard criteria, dividing it into four categories from TRG 1-4, based on the proportion of residual tumor and fibrotic tissue. This classification is more accurate than evaluating downstaging T, as was done in our study.

5. Conclusion

According to our study's results, ΔADC values before and after treatment have potential prognostic value in rectal cancer patients after nRCT, providing more accurate diagnostic information than tumor volume. Drawing the ROI on the slice with the largest tumor area is a time-saving method that retains diagnostic value and can be applied in clinical practice.

Proposed direction for further research: Conducting the study on a larger sample size and employing total neoadjuvant treatment, evaluating the pathological response post-surgery using the Mandard criteria.

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