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ORIGINAL ARTICLE

Prognostic Significance of Diffusion-Weighted Imaging in T-Staging of Rectal Cancer and Its Association with 18F-FDG PET/CT Parameters

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Abstract

Background: This study aimed to investigate the relationship between the apparent diffusion coefficient (ADC) derived from diffusion-weighted imaging (DWI) and metabolic parameters obtained from 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) across different T-stages in patients with rectal cancer (RC), and to evaluate the prognostic significance of these imaging biomarkers for survival outcomes.

Methods: This retrospective study included patients with non-mucinous rectal adenocarcinoma who underwent both pelvic magnetic resonance imaging (MRI) and 18F-FDG PET/CT before treatment. T-staging was performed using T2-weighted magnetic resonance imaging images, and ADC measurements were obtained from DWI. Metabolic tumor parameters, including maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), were obtained from PET/CT images. A correlation analysis was performed between ADC and 18F-FDG PET/CT parameters and the T-stage. ROC curve analysis was performed to evaluate the diagnostic performance of ADC and 18F-FDG PET/CT parameters in the early T stage. Overall survival (OS) and progression-free survival (PFS) were estimated and analyzed.

Results: A moderate negative correlation was found between T-stage and ADC ($r = -0.43$, $p = 0.003$), and a low-moderate positive correlation was found between TLG and ADC ($r = 0.33$, $p = 0.027$). ADC showed good diagnostic performance in identifying early T-stage tumors (AUC = 0.86; cutoff = 864×10^{-6} mm²/s). The OS in the low ADC group was 58.1±6.5 (45.3-70.9) and in the high ADC group 97.4±10.9 (76.1-110.8). PFS was 53.7±5.9 (42.1-65.1) in the low ADC group and 93.3±10.4 (73.0-113.6) in the high ADC group. OS ($p = 0.018$) and PFS ($p = 0.042$) were longer in the high ADC group, indicating a statistically significant association.

Conclusion: ADC showed a significant association with both tumor stage and survival outcomes and may serve as a noninvasive prognostic biomarker in non-mucinous rectal adenocarcinoma. Although TLG correlated with T stage, PET/CT-derived metabolic parameters did not predict survival. These findings support the potential role of DWI in pre-treatment risk stratification.

Keywords: Apparent diffusion coefficient, total lesion glycolysis, survival analysis, rectal cancer.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers and the second leading cause of cancer-related deaths. Rectal cancer (RC) accounts for approximately 30–40% of all CRC cases (1). Despite improvements in diagnosis and treatment, the death rate for CRC has dropped; however, the outlook for RC remains worse due to frequent local recurrence and distant spread (2). The prognosis for RC is usually based on tumor node metastasis (TNM) staging, which is seen as the most important factor for predicting outcomes (3). Still, TNM staging is especially poor at predicting metastatic risk at stage 2 (4,5). Because of this, there is a need for new prognostic markers.

Magnetic resonance imaging (MRI) is frequently used, particularly for local staging, whereas fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG PET/CT) is commonly utilized for detecting distant metastases and systemic staging (6). In recent years, both MRI and 18F-FDG PET/CT have demonstrated the ability to provide important information beyond just staging. With advancements in MRI technology, diffusion-weighted imaging (DWI) has been employed to measure the Brownian motion of water molecules (7). The movement of water molecules is inversely proportional to cellular density. The quantitatively measured apparent diffusion coefficient (ADC) from DWI is used to assess various solid tumors (8). Recently, ADC has been proposed as a parameter that may aid in indicating tumor aggressiveness in RC (9). However, due to challenges in measuring ADC values and the absence of standardized thresholds, its application in staging RC remains limited (10). Further studies are needed to identify suitable applications and time points for ADC values in RC.

18F-FDG PET/CT is used to detect metastases in CRC (11). 18F-FDG PET/CT imaging measures the maximum standardized uptake value (SUVmax) to indicate metabolic activity, metabolic tumor volume (MTV) to represent metabolic volume, and total lesion glycolysis (TLG) to reflect both metabolic activity and volüme (12). All three parameters are associated with prognosis in RC (12). In patients with RC, it has been observed that those with lower FDG uptake values, as measured by SUVmax, survive longer (13). Another study suggests longer survival in patients with a lower MTV value (14).

While MRI and 18F-FDG-PET/CT imaging have been studied separately in various investigations of RC, the relationship between DWI-derived ADC values and 18F-FDG-PET/CT-derived parameters, such as SUVmax, MTV, and TLG, with T-stage and survival has not been examined together. Therefore, this study aims to investigate the association between MRI- and 18F-FDG-PET/CT-derived parameters and T-stage and survival in RC.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective study was approved by the institutional ethics committee (decision no. 2024-01/03, date: 18.01.2024) and conducted in accordance with the Declaration of Helsinki. Patients histopathologically diagnosed with non-mucinous rectal adenocarcinoma between September 2014 and October 2023 who underwent both pelvic MRI and 18F-FDG PET/CT before any treatment were included. Exclusion criteria were mucinous adenocarcinoma or other histologic subtypes, coexistence of another malignancy, prior neoadjuvant chemoradiotherapy, and inadequate imaging quality due to motion or technical artifacts on MRI or PET/CT. All MRI and PET/CT examinations were performed using the same standardized imaging protocols consistently over the entire 9-year study period, ensuring comparability of measurements.

MRI Protocol and ADC Calculation

All patients underwent MRI for the primary tumor before surgery or neoadjuvant chemoradiotherapy. Patients were informed about slow breathing before imaging. All images were obtained using a 1.5 Tesla MRI machine (Siemens Magnetom, Erlangen, Germany) with a phased-array body coil. In all patients, T1-weighted (TR/TE 640/6 ms, FOV 320 × 320 mm, matrix 384x288, slice thickness 5 mm, skip 1 mm), T2-weighted (TR/TE 7200/168 ms, FOV 240 × 240 mm, matrix 320x288, slice thickness 5 mm and skip 1 mm), contrast fat suppressed T1(TR/TE 4.1/1.1 ms, FOV 320 × 320 mm, matrix 288x192, slice thickness 3 mm, skip 1.5 mm) and DWI with b-values of 0 and 1000 s/mm². ADC maps were generated automatically.

Local tumor staging is conducted according to the TNM classification and the classification of the International

Union Against Cancer (UICC) using T2-weighted images acquired in three planes: axial, sagittal, and coronal. The T1 tumor is confined to the mucosa and submucosa, while the T2 tumor has invaded the muscularis propria. The T3 tumor has exceeded the muscularis propria, and the T4 tumor has invaded the peritoneal surface or adjacent organs (15). Staging relies on clinical information, pathologic findings, and two radiologists who were unaware of each other. In cases of discrepancy, a joint assessment was conducted, leading to a consensus conclusion. ADC values were measured by manually placing three circular regions of interest (ROIs) on the largest solid area of the tumor on ADC maps, avoiding necrotic or hemorrhagic regions based on T2-weighted and post-contrast images. Two radiologists with more than five years of experience independently performed ADC measurements while blinded to clinical and pathological findings. The mean ADC value for each tumor was calculated by averaging the three ROIs and then averaging the measurements from both radiologists (16).

PET/CT Protocol and Quantitative Analysis

18F-FDG PET/CT imaging was performed using a hybrid PET/CT system (Discovery 600, GE Healthcare, USA). All patients fasted for at least 6 hours before imaging, and blood glucose levels were confirmed to be less than 180 mg/dL before injection. Images were acquired 60 minutes after intravenous administration of 18F-FDG. Low-dose CT was used for attenuation correction (120 kV, 70 mA, slice thickness 2.5 mm), followed by PET acquisition from the skull base to the mid-thigh (2 minutes per bed position, 3D mode).

Quantitative metabolic parameters were calculated by placing a 3D region of interest over the primary tumor. The following PET metrics were recorded:

- SUVmax: maximum standardized uptake value within the tumor
- MTV: metabolic tumor volume calculated above a threshold of 42% of SUVmax
- TLG: total lesion glycolysis calculated as SUVmean × MTV.

Follow-up and Outcomes

Patient data were collected from clinical records, including age, sex, recurrence, metastasis, and survival status. Overall survival (OS) was defined as the time from diagnosis to death from any cause or last follow-up. Progression-free survival (PFS) was defined as the time from diagnosis to local recurrence, distant metastasis, or death.

Statistical Analysis

The sample size was estimated using the G-Power 3.1.9.4 software. Based on an assumed effect size of 0.40, a type I error rate (α) of 0.05, and a statistical power of 80%, it was determined that a minimum of 40 participants would be required for the study. SPSS v. 22 (IBM, USA) software was used for data analysis. Normal distribution was assessed using the Kolmogorov-Smirnov test. If the numerical values were normally distributed, they were presented as mean ± standard deviation; if not normally distributed, they were presented as median (min-max). Inter-observer reliability for ADC measurements between the two independent observers was assessed using the intraclass correlation coefficient (ICC). The ICC values were interpreted as follows: <0.50, poor; 0.50–0.75, moderate; 0.75–0.90, good; and >0.90, excellent reliability. Spearman correlation estimates were employed to compare frequency distributions between groups. The diagnostic performance of ADC at T-stage was evaluated using receiver operating characteristic (ROC) curve analysis. The cutoff value of ADC was determined using the Youden index method in ROC curve analysis. The relationship between ADC and the data was assessed using the Chi-square, Fisher's Exact, Mann-Whitney U, and Kruskal-Wallis tests. OS and PFS were estimated using the Kaplan-Meier method and analyzed with a log-rank test. A value of $p \leq 0.05$ was considered significant.

RESULTS

A total of 51 patients diagnosed with rectal cancer were initially evaluated. Eight patients were excluded due to incomplete imaging or clinical data, leaving 43 patients in the final analysis. The median age was 70.0±10.7 years (range: 37-89). Among the patients, 25 (58.1%) were male. The distribution of T-stage was as follows: 14% were T1, 27.9% were T2, 48.8% were T3, and 9.3% were T4. Eighteen patients had distant metastases. The mean values were as follows: TLG 234.5±183.7, MTV 27.6±20.7, SUVmax 14.8±4.9. The inter-observer relia-

bility for ADC measurements showed excellent agreement, with an ICC value of 0.92 (95% CI: 0.88–0.95).

Correlation analysis was performed between T-stage and the parameters ADC, SUVmax, MTV, and TLG in RC patients. A moderate negative correlation was found between T-stage and ADC (r = -0.436, p = 0.003), and a low-moderate positive correlation was found between T-stage and TLG (r = 0.337, p = 0.027), both statistically significant. No significant correlations were found between ADC and SUVmax, MTV, or TLG (p> 0.05) (Table 1).

Receiver operating characteristic (ROC) analysis showed that ADC had good diagnostic performance in differentiating early T-stage (T1) tumors, with an area under the curve (AUC) of 0.86 (95% CI: 0.55–0.88). The optimal cutoff value for ADC was 864 × 10^{-6} mm^2/s, based on the Youden index. Using this cutoff, 26 patients (60.5%) were classified in the low ADC group and 17 patients (39.5%) in the high ADC group. No statistically significant associations were found between ADC and other parameters (Table 2) (Figure 1).

Table 1. Spearman Correlation Analysis Between T-stage and the Parameters ADC, SUVmax, MTV, and TLG in Rectal Cancer

		ADC	SUVmax	MTV	TLG
T stage	**Correlation Coefficient**	-0.436	-0.018	0.293	0.337
	P value	0.003*	0.908	0.057	0.027*
	N	43	43	43	43

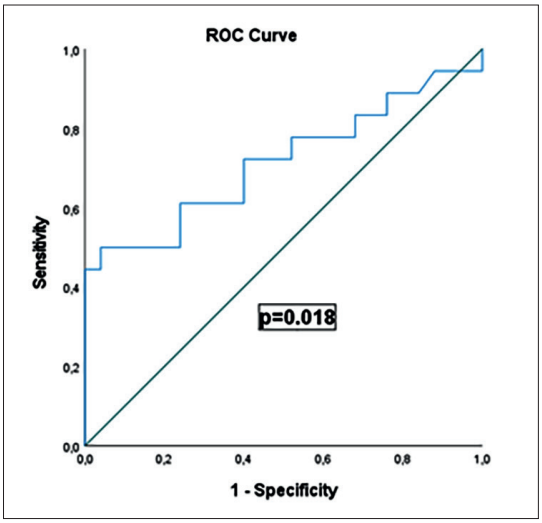


Figure 1: ROC curve showing the diagnostic performance of early-stage rectal cancer (T1)

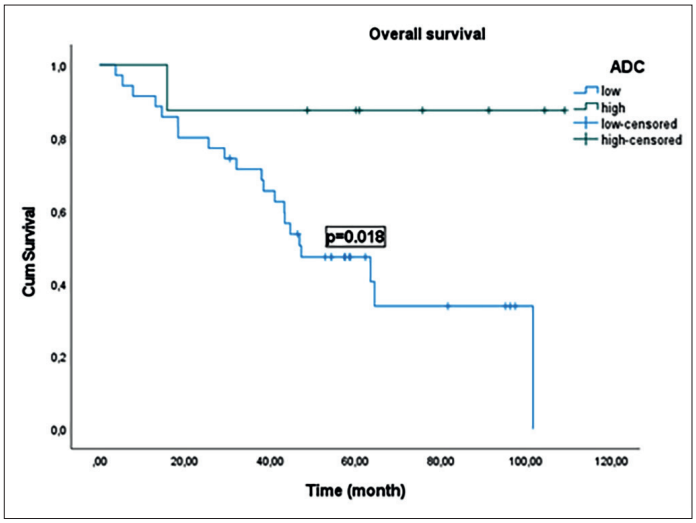


Figure 2: Relationship between ADC and overall survival in rectal cancer

During a median follow-up period of 51.4 months (95% CI: 3.7-109.7 months), 22 patients (51.2%) died, and 7 patients (16.3%) experienced progression. The median OS was 66.9±6.3 months (54.6-79.3 months). The OS was 58.1±6.5 months (45.3-70.9 months) in the low ADC group and 97.4±10.9 months (76.1-110.8 months) in the high ADC group. OS was significantly longer in the high ADC group, with a statistically significant association (p = 0.018) (Figure 2).

The median PFS was 62.2±6.2 months (50.2-74.0 months). PFS was 53.7±5.9 months (42.1-65.1 months) in the low

Table 2. Evaluation of the Relationship Between ADC and Blinical and PET-CT Parameters

	ADC(10-6 mm2/s)		
Variable	**Low(<864) (Mean±SD)**	**High(≥864) (Mean±SD)**	**P value**
Age(years)	67,1±1,9	66,4±3,1	0,238
TLG(g.cm3/mL)	227,6±30,3	264,4±75,1	0,901
MTV(cm3)	27,7±3,7	27,1±6,1	0,576
SUVmax (g/mL)	14,5±0,8	15,9±1,7	0,682
Gender			
Male	21(%60,0)	4(%50,0)	0,447
Female	14(%40),0	4(%50,0)	
T stage			
1	0(%0)	6(%75,0)	<0,0001*
2	11(%28,6)	2(%25,09	
3	20(%60,0)	0(%0)	
4	4(%11,4)	0(%0)	
Metastasis			
No	18(%51,4)	7(%87,5)	0,067
Yes	17(%58,8)	1(%12,5)	
*p<0.05: Statistically significant			

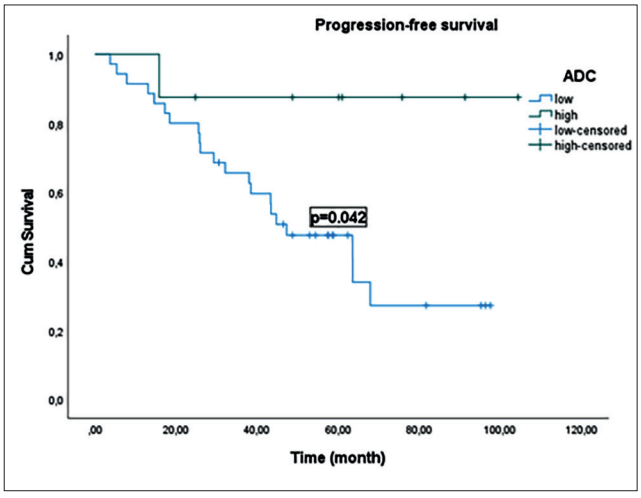


Figure 3: Relationship between ADC and progression-free survival in rectal cancer

ADC group and 93.3±10.4 months (73.0-113.6 months) in the high ADC group. PFS was significantly longer in the high ADC group, with a statistically significant association (p = 0.042) (Figure 3).

None of the PET/CT metabolic parameters (SUVmax, MTV, or TLG) showed a statistically significant association with OS or PFS (p> 0.05).

DISCUSSION

MRI and 18F-FDG PET/CT are widely used imaging modalities for evaluating rectal cancer, providing complementary anatomic and functional information. In recent years, there has been growing interest in quantitative imaging biomarkers as prognostic tools that reflect

tumor biology beyond conventional TNM staging. In this study, we investigated the relationship between the ADC derived from diffusion-weighted MRI and metabolic parameters from 18F-FDG PET/CT in patients with non-mucinous rectal adenocarcinoma. Correlations were found between ADC and TLG with T-stage. In addition, ADC was found to have independent predictive value for OS and PFS.

Diffusion-weighted imaging and 18F-FDG PET/CT are commonly used imaging modalities in the evaluation of cancer. Reduced ADC and increased SUV values are usually observed in tumors. Additionally, DWIs combined with T2 images and 18F-FDG PET/CT images have been shown to have a potential role in predicting tumor response to treatment in addition to diagnosis (6). TNM staging is crucial for predicting prognosis. In many studies, DWI has been used to predict T-stage (3). Hu et al. (17) found a negative correlation and a statistically significant difference between pathological T stage and ADC based on the largest tumor diameter. Similarly, in our study, we found a negative correlation and a statistically significant difference between T stage and ADC. These results can be explained by the cellular density and histologic intensity within the tumor (18). Based on these results, we hypothesize that tumors with low ADC values may be associated with higher stages and greater aggressiveness.

SUV values in 18F-FDG PET/CT reflect the activity of FDG uptake in tumor tissue. SUV values have been found to correlate with tumor cell density, grade, and differentiation of the tumor. The studies cited by Hu et al. (17) have reported correlations between T-stage and parameters such as SUVmax, MTV, and TLG. However, in a study by Kido et al. (19), no correlation was found between SUVmax and MTV with T stage; only TLG showed a correlation with T stage. This discrepancy is attributed to the heterogeneous low-density proliferation associated with different histologic types of RC, which can invade deeper tissues. TLG is thought to be more indicative of tumor invasion than traditional SUVmax, as it may reflect glucose metabolism in poorly differentiated invasive cancers with minimal morphological changes. Similarly, in our study, no significant correlation was found between T-stage and SUVmax or MTV, whereas TLG demonstrated a statistically significant association.

Many studies have investigated the relationship between ADC and survival in RC, but no consensus has been reached (20). In a recent study by Zhang et al. (21), ADC was found to be an independent predictor of 5-year PFS but not OS. Another study showed that preoperative low ADC levels are associated with disease-free survival (22). In our study, we found that patients with low ADC scores had shorter OS and PFS, while those with high ADC scores had longer OS and PFS. We believe that this is due to the decrease in ADC levels associated with increased cell density and the resulting increase in tumor aggressiveness.

In rectal cancer, 18F-FDG PET/CT imaging has been extensively studied for prognostic analysis before or after neoadjuvant therapy. Studies investigating the prognostic significance of pre-treatment 18F-FDG PET/CT imaging parameters have provided conflicting results (12). Some studies have found no association between 18F-FDG PET/CT parameters and prognosis (12,23,24). Conversely, some studies have identified significant correlations between 18F-FDG PET/CT parameters and survival. However, these studies have also demonstrated that significant parameters may vary in different tissues, such as the primary tumor, lymph nodes, and even bone marrow (12,25,26). In addition, survival outcomes determined by ROC analysis also vary across these studies (12). In this study, we found no correlation between the 18F-FDG PET/CT parameters and survival. It is assumed that the differing results of the individual studies are due to the varying inclusion criteria and clinical stages. We believe that prospective studies with larger and more homogeneous patient populations are needed to clarify these discrepancies and establish more reliable prognostic markers.

Contrary to some previous studies reporting significant inverse correlations between ADC and metabolic PET parameters (27), our results did not demonstrate a significant relationship between ADC and SUVmax, MTV, or TLG. This cohort included only non-mucinous rectal adenocarcinomas, which reduces histopathological heterogeneity, but other technical factors may contribute to the observed discrepancy. Variations in MRI and PET/CT acquisition protocols and ROI placement could affect measurements independently, thereby weakening the expected correlation. These findings highlight the need for standardized imaging protocols and larger multicenter studies to better clarify the relationship between diffusion and metabolic parameters in rectal cancer.

This study has several limitations. First, it uses a retrospective design and has a relatively small sample size, which may limit the generalizability of the findings. However, the sample size is comparable to those in similar imaging biomarker studies in rectal cancer (21, 22). Second, although ADC showed a significant association with survival, multivariate Cox proportional hazards analysis could not be performed because of the limited number of survival events, preventing confirmation of ADC as an independent prognostic factor. Third, including only non-mucinous adenocarcinomas reduces heterogeneity but may limit applicability to the broader rectal cancer population. Fourth, although imaging protocols were standardized, inter-institutional variability could not be assessed due to the single-center design. Fifth, due to the relatively small number of events, we were unable to provide confidence intervals and risk tables for survival curves without risking unreliable estimates. Finally, while an ADC cut-off of 864 was identified in this study, its generalizability to other centers remains uncertain, and external validation in larger, multicenter cohorts is needed to confirm the robustness and applicability of this threshold.

Apparent diffusion coefficient values derived from DWI show a significant inverse relationship with T-stage and are independently associated with OS and PFS in RC patients. While TLG correlates with T-stage, other PET/CT metrics do not demonstrate prognostic significance. These findings support incorporating ADC into pre-treatment imaging evaluation to improve prognostic assessment and guide clinical decision-making. Future prospective multicenter studies with larger sample sizes are needed to validate these results and standardize the clinical use of ADC in rectal cancer.

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Abbreviations List

ADC: Apparent Diffusion Coefficient
AUC: Area Under the Curve
DICOM: Digital Imaging and Communications in Medicine
DWI: Diffusion-Weighted Imaging
FOV: Field of View
MTV: Metabolic Tumor Volume
OS: Overall Survival
PFS: Progression-Free Survival
ROI: Region of Interest
SUVmax: Maximum Standardized Uptake Value
SUVmean: Mean Standardized Uptake Value
TLG: Total Lesion Glycolysis
UICC: Union for International Cancer Control

Ethics Approval and Consent to Participate

This study was approved by the Non-Interventional Clinical Trials Ethics Committee of Sivas Cumhuriyet University on 18.01.2024 with decision number 2024-01/03.

Consent for Publication

There is no personal data of any person in the study.

Availability of Data and Materials

The study data is stored digitally. It is in the hospital information system and is not publicly available due to the protection of personal data. However, for scientific reasons, it can be made available upon request by the corresponding author.

Competing Interests

The authors declare that they have no conflict of interest.

Funding

No funding was used in the study.

Authors Contributions

Idea/Concept: IA, ZH, MY Desıgn: IA, ZH, EG. Control/Supervısıon IA, ZH, MA. Data Collectıon And/Or Processıng: IA, MY, EG, ROY. Analysıs And/Or Interpretatıon: IA, MA, ROY. Lıterature Revıew: IA, ZH, EG. Wrıtıng The Artıcle: IA. Crıtıcal Revıew: IA, ZH, MA, EG.

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