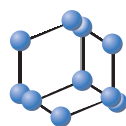
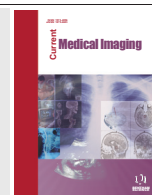


RESEARCH ARTICLE


**BENTHAM
SCIENCE**

Complete Response Evaluation of Locally Advanced Rectal Cancer to Neoadjuvant Chemoradiotherapy Using Textural Features Obtained from T2 Weighted Imaging and ADC Maps



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Abstract: Background: The prediction of pathological responses for locally advanced rectal cancer using magnetic resonance imaging (MRI) after neoadjuvant chemoradiotherapy (CRT) is a challenging task for radiologists, as residual tumor cells can be mistaken for fibrosis. Texture analysis of MR images has been proposed to understand the underlying pathology.

Objective: This study aimed to assess the responses of lesions to CRT in patients with locally advanced rectal cancer using the first-order textural features of MRI T2-weighted imaging (T2-WI) and apparent diffusion coefficient (ADC) maps.

Methods: Forty-four patients with locally advanced rectal cancer (median age: 57 years) who underwent MRI before and after CRT were enrolled in this retrospective study. The first-order textural parameters of tumors on T2-WI and ADC maps were extracted. The textural features of lesions in pathologic complete responders were compared to partial responders using Student's t- or Mann-Whitney U tests. A comparison of textural features before and after CRT for each group was performed using the Wilcoxon rank sum test. Receiver operating characteristic curves were calculated to detect the diagnostic performance of the ADC.

Results: Of the 44 patients evaluated, 22 (50%) were placed in a partial response group and 50% were placed in a complete response group. The ADC changes of the complete responders were statistically more significant than those of the partial responders ($P = 0.002$). Pathologic total response was predicted with an ADC cut-off of $1310 \times 10^{-6} \text{ mm}^2/\text{s}$, with a sensitivity of 72%, a specificity of 77%, and an accuracy of 78.1% after neoadjuvant CRT. The skewness of the T2-WI before and after neoadjuvant CRT showed a significant difference in the complete response group compared to the partial response group ($P = 0.001$ for complete responders vs. $P = 0.482$ for partial responders). Also, relative T2-WI signal intensity in the complete response group was statistically lower than that of the partial response group after neoadjuvant CRT ($P = 0.006$).

Conclusion: As a result of the conversion of tumor cells to fibrosis, the skewness of the T2-WI before and after neoadjuvant CRT was statistically different in the complete response group compared to the partial response group, and the complete response group showed statistically lower relative T2-WI signal intensity than the partial response group after neoadjuvant CRT. Additionally, the ADC cut-off value of $1310 \times 10^{-6} \text{ mm}^2/\text{s}$ could be used as a marker for a complete response along with absolute ADC value changes within this dataset.

Keywords: Rectum MRI, computer aided-detection, tissue characterization, textural features, locally advanced rectal cancer, apparent diffusion coefficient (ADC).

1. INTRODUCTION

Colorectal cancer is the third most common cancer among men and the second most common cancer among

women worldwide [1]. It was ranked third for the number of cancer-related deaths in male and female patients in 2020 [2]. The prognosis of rectal cancer is associated with the infiltration of tumors into the mesorectum and the ability to achieve negative circumferential resection margins [3]. The traditional treatment option for rectal cancer is total mesorectal excision (TME), and the increasing use of neoadjuvant chemoradiotherapy (CRT) in locally advanced

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rectal cancer shows promising results for local disease control [4, 5]. According to current guidelines, neoadjuvant CRT followed by TME is the gold standard for the treatment of patients diagnosed with locally advanced rectal cancer [4, 5]. Approximately half of the locally advanced rectal cancer shows signs of regression after neoadjuvant CRT, and nearly one-third of patients have a complete pathologic response after concomitant TME [4]. Several studies have demonstrated that patients who show complete pathologic response to neoadjuvant CRT can be monitored with a rectal sparing approach due to low local recurrence rates, long-term survival, and high sphincter protection rates [6-9]. However, patients with locally advanced rectal cancer exhibit substantial individual differences in response to neoadjuvant CRT [10, 11]. Therefore, the identification of patients who show complete response to neoadjuvant CRT might prompt clinicians to adopt a “watch and wait” strategy to avoid overtreatment, which carries the risk of major complications and the severe impairment of bowel function [6, 12, 13].

Magnetic resonance imaging (MRI) is widely used to evaluate treatment response after neoadjuvant CRT with digital rectal examination and endoscopy. The two most visible signs of treatment response in MRI T2-weighted imaging (T2-WI) are a reduction in volume and fibrotic transformation. Although MRI has been successfully used in primary rectal cancers, it has some limitations in assessing treatment response. These limitations arise from the difficulty in distinguishing residual living cells from fibrosis, desmoplastic reactions, and colloid in conventional morphological assessments [14, 15]. The residual tumor risk in fibrotic areas is known to be approximately 50% [16-19], and various methods based on a visual assessment of MRI have been proposed to distinguish fibrosis from the residual tumor. For a few years, MRI tumor regression grading (mrTRG), similar to the Dworak tumor regression grade system [20], has been recommended [20-23]. Recently, the use of mrTRG has been largely discontinued due to mrTRG showing a weak relationship with pathological response [24]. Another method, MRI T2-W volumetry, has been investigated for identifying pathologic complete response. However, its diagnostic performance is inconsistent: one study revealed no significant difference in post-treatment tumor volume between complete and partial response patients ($P = 0.451$), while others observed complete responses ranging from 0.700 to 0.792 area under the curve [16, 18, 25]. Therefore, a new non-invasive method based on MRI signal intensity distribution beyond visual assessment has recently been investigated. Texture analysis, a non-invasive method for assessing tumor lesion heterogeneity, measures the distribution of signal intensities on a pixel-by-pixel basis [26]. Used with MRI, it provides a measure of the uniformity and coarseness within a lesion and can help practitioners distinguish underlying patterns and pathologies [27]. Several studies investigating local advanced rectal cancer have shown that texture analysis derived from an apparent diffusion coefficient (ADC) map effectively predicted neoadjuvant CRT response [28, 29]. In addition to the textural features derived from ADC mapping, other studies have suggested that textural parameters based on T2-WI could also be used to identify complete response to neoadjuvant CRT

[30]. Therefore, we speculated that an effective combination of textural features obtained from T2-WI and ADC mapping could determine pathologic complete response with considerable predictive precision. Accordingly, this study aimed to investigate whether quantitative multimodal MRI data based on first-order textural features can predict treatment outcomes in patients with locally advanced rectal cancers after neoadjuvant CRT.

2. MATERIALS AND METHODS

The research procedure was approved by the Institutional Review Board of the Istanbul Faculty of Medicine, Istanbul University, and informed consent from patients was waived due to the study's retrospective nature.

2.1. Patients

From April 2015 to April 2019, 216 consecutive patients with histopathological proven rectal adenocarcinoma were retrospectively evaluated. The following inclusion criteria were used: i) patients with locally advanced rectal cancer (higher than stage T2) demonstrated by MRI before neoadjuvant CRT; ii) patients who underwent rectal MRI, including diffusion-weighted images (DWI), before and after neoadjuvant CRT; and iii) patients who had long-course neoadjuvant CRT followed by surgical resection or endoscopic evaluation and concomitant biopsy. The inclusion and exclusion criteria are summarized in Fig. (1).

All the patients were treated with preoperative concurrent chemoradiotherapy. Radiation therapy was performed with a total dose of 50.4 Gy (1.8–2 Gy/per fraction daily, 5 days a week over 5 weeks) to planned target volumes, including tumors and pelvic lymph nodes. Radiation therapy also included synchronous integrated boost therapy to the gross tumor within the same period. Chemotherapy was concurrently performed with 425 mg/m²/d of 5-fluorouracil and 20 mg/m²/d of leucovorin during weeks 1 and 5 of radiation therapy or as capecitabine 825 mg/m², 5 days a week for 5 weeks. Surgical resection or endoscopic evaluation and concomitant biopsy were usually performed 6–8 weeks after the completion of neoadjuvant CRT.

2.2. MRI Acquisition

All patients were examined using a 1.5 Tesla MR scanner (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany and Philips Achieva, Best, Nederland) before and after neoadjuvant CRT (approximately 1 week before surgery). All the patients underwent bowel preparation with glycerin enemas before undergoing MRI. They were placed in a supine position, and a phased-array body coil was used for the imaging. The MRI protocol consisted of sagittal turbo spin echo (TSE) T2-WI (TR/TE = 3200/100 ms; FOV: 280 × 280; matrix: 348 × 280; slice thickness: 3 mm); oblique para-axial (perpendicular to the longitudinal axis of the tumor) TSE T2-WI (TR/TE = 3000/100 ms; matrix = 348 × 278; FOV = 210 × 228 mm; slice thickness = 3 mm); para-coronal TSE T2-WI (TR/TE = 3200/100 ms; matrix = 348 × 280; FOV = 280 × 280 mm; slice thickness = 3 mm); and para-axial DWI (TR/TE = 5400/53 ms; matrix = 250 ×

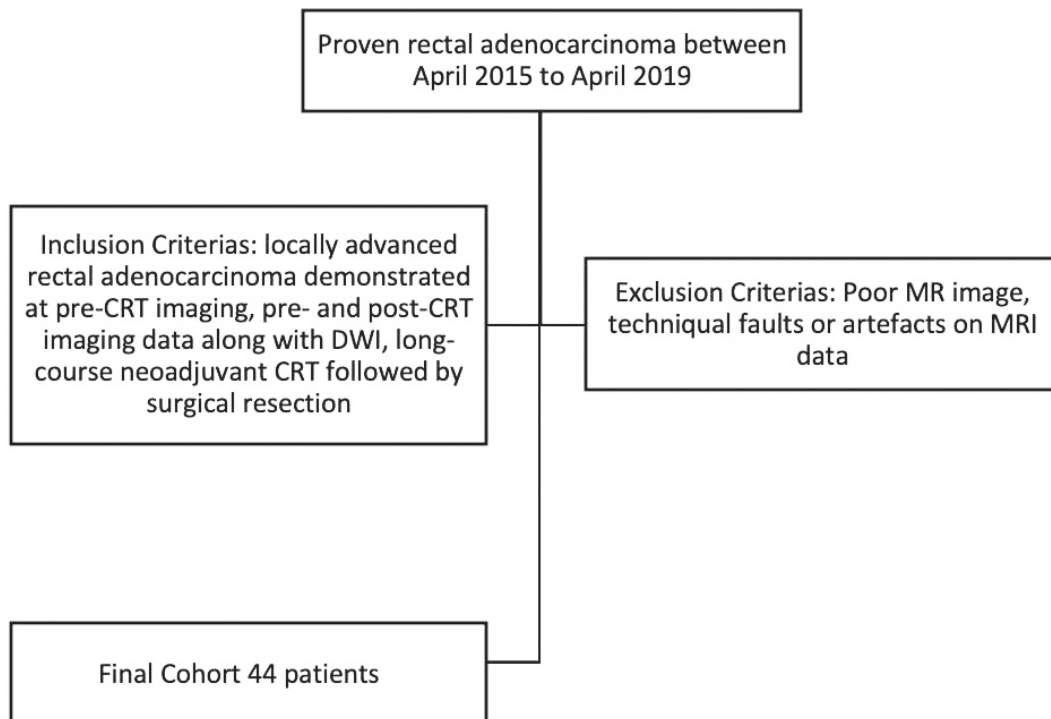


Fig. (1). The inclusion and exclusion criteria.

200; FOV = 350 × 306 mm; slice thickness = 4 mm; using three b values, 0, 500, and 1000 s/mm²). ADC maps were automatically generated using a mono-axial decay model using the three b values.

2.3. Histopathological Evaluation

Histopathological evaluation was accepted as the gold standard for the MRI findings. The percentage of residual tumors evident on microscopic examination of surgically or endoscopically resected specimens was evaluated by a pathologist. The tumor regression grade was evaluated according to the system described by Dworak *et al.* [20]. The tumor regression grade was histopathologically graded as follows: grade 0 indicated no regression, grade 1 (minimal regression) indicated a dominant tumor mass with obvious fibrosis and/or vasculopathy, grade 2 (moderate regression) indicated dominantly fibrotic changes with few tumor cells or groups, grade 3 (near-total regression) indicated very few tumor cells in fibrotic tissue with or without mucous substance, and grade 4 indicated total regression.

2.4. MRI Data Analysis

A board-certified abdominal radiologist with 10 years of experience in rectal imaging reviewed the T2-W rectal images and the DWIs before and after neoadjuvant CRT. Primary and residual tumors were defined as intermediate signal areas, compared to the hypointense signal of adjacent normal muscle rectal wall in T2-W images and the high signal intensity areas on high b values. After neoadjuvant CRT, areas with significantly lower signal intensity at the location of the primary tumor bed in the T2-W images and low signal intensity areas on high b values were interpreted as fibrosis. When performing the texture analysis, measure-

ments were also taken from the fibrous areas because the residual tumor risk in these fibrotic areas is known to be approximately 50% [16-19]. The T2-W images were used as a reference for tumor placement before and after neoadjuvant CRT.

2.5. Region of Interest Delineation and Histogram Analysis

The same abdominal radiologist with 10 years of clinical experience in the interpretation of rectal MRI delineated each tumor with a polygonal region of interest (ROI) on axial T2-W images before and after neoadjuvant CRT. Relative T2-WI signal intensity was used to normalize the T2-WI signal intensity due to the possibility of arbitrary units differing between study visits and subjects. The relative T2-WI signal intensity was obtained by dividing the signal intensity of the tumor area by the signal intensity of the obturator internus muscle region of the healthy side. The ROI was selected at the level of the largest tumor area depicted on the axial T2-W images. The obturator internus of the healthy side was delineated with the same sized polygonal ROI on axial T2-W images to calculate the relative T2-WI signal intensity. Any area suspected of being necrotic or a cystic lesion was excluded from the ROI. The ROI of the axial T2-WI was located first and then the same ROI was copied to the ADC maps; therefore, the same area was delineated in all sequences of the before and after neoadjuvant CRT. For whole and residual tumor volume calculations, all slices were delineated on T2-W images before and after neoadjuvant CRT. The whole and residual tumor volumes were automatically calculated using OsiriX software (Pixmeo, Switzerland). The ROI textural parameters were obtained using OsiriX. First-order textural features, including skewness, kurtosis, and mean signal intensity values, were

RegionArea: 61.578 mm², 496 pixels

Mean: 40.788 Median: 41.000 SDev: 14.691 Sum: 20,231

Min: 3.000 Max: 104.000 Skewness: 0.672 Kurtosis: 2.012

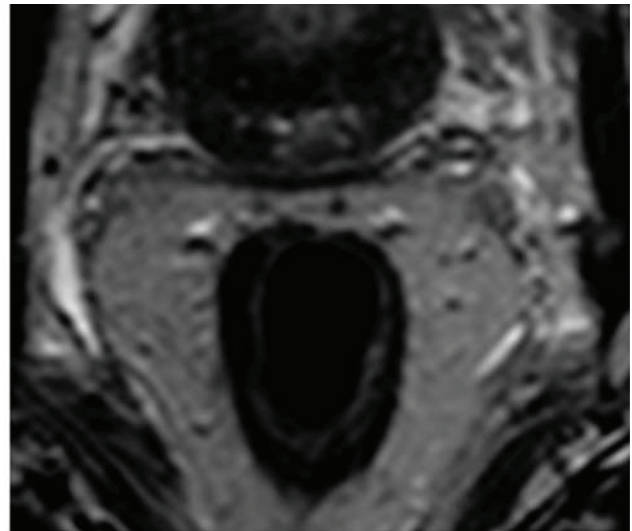
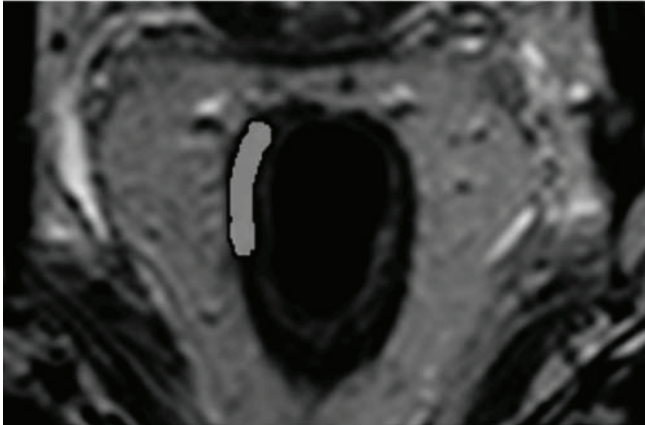


Fig. (2). Region of interest delineation and textural features of locally advanced rectum cancer after neoadjuvant chemoradiotherapy. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

obtained from the ADC and T2-W images. They were then used to evaluate textural feature changes after neoadjuvant CRT (Fig. 2).

2.6. Statistical Analysis

The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for the statistical analysis. Descriptive statistical parameters (*i.e.*, mean, standard deviation [SD], median, frequency, percentage, minimum, and maximum) were used to evaluate the data. Normal distribution was tested using the Shapiro–Wilk test, Student’s t-test was used to compare the values of normally distributed quantitative variables, and the Mann–Whitney U test was used to compare the quantitative variables that were not normally distributed between the complete responders and the partial responders. Normally distributed pretreatment and post-treatment values were compared using a paired t-test, whereas the values of variables that were not normally distributed were compared using the Wilcoxon rank-sum test. Qualitative data were compared using the Fisher-Freeman-Halton test. Receiver operating curve (ROC) analysis was used to determine the cut-off point of the ADC values. The threshold for determining statistical significance was set at $P < 0.05$.

3. RESULTS

3.1. Clinical Characteristics

The study cohort consisted of 44 patients: 32 male (72.2%) and 12 female (27.3%) with a mean age of 56.5 years (SD = 10.9). The demographic features of the study cohort are presented in Table 1. There were no statistical differences between the ages of the patients and tumor localization in the complete response and partial response groups ($P = 0.588$ for age and $P = 0.550$ for localization). Residual tumors were confirmed by histological demonstration in 22 (50%) patients. The remaining patients were complete responders, according to histopathological evaluation. Five of

the complete responders were identified using surgical resection, while 17 were identified using endoscopic biopsy. The local recurrence rate for complete responders at follow-up examinations was 5/17 (29.4%) (Table 1).

3.2. Textural Features

The absolute ADC value was significantly higher after neoadjuvant CRT ($P < 0.001$), while the whole tumor volume and relative T2-WI signal intensity were significantly lower after neoadjuvant CRT ($P < 0.001$) in all patients. The skewness of T2-WI significantly increased after CRT in all patients ($P = 0.004$), but the kurtosis did not significantly change. In contrast, there were no significant changes in the kurtosis or skewness of the ADC maps after neoadjuvant CRT (Table 2).

The primary tumor volumes in the partial responders (50.55 ± 37.01 cm³) were significantly higher ($P < 0.001$) than those in the complete responders (17.07 ± 11.32 cm³), as shown in Table 3. The partial and complete responders did not show any significant differences in their ADC values before neoadjuvant CRT. However, after neoadjuvant CRT, the ADC-value change was significantly higher ($P = 0.002$) in the complete responders ($572.1 \pm 264.7 \times 10^{-6}$ mm²/s) than in the partial responders ($353 \pm 170.7 \times 10^{-6}$ mm²/s). According to the ROC analysis, the post-CRT cut-off ADC value for differentiation between the partial and complete responders was 1310.02×10^{-6} mm²/s, with sensitivity, specificity, and accuracy values of 72.73%, 77.27%, and 78.1%, respectively. The post-CRT relative signal intensity of the T2-W images was significantly lower ($P = 0.006$) for the complete responders (1.81 ± 0.60) compared to the partial responders (2.52 ± 0.99) (Table 3). The skewness and kurtosis values in the ADC maps for both groups before and after the CRT were not significantly different. Neoadjuvant CRT significantly increased the skewness of the T2-W signal intensity values in the complete responders, but not in the partial responders ($P = 0.001$ vs. $P = 0.482$ respectively). However, kurtosis changes in the T2-WI signal intensity

Table 1. Demographic characteristics of locally advanced rectal tumor.

-	-	Number of Subjects (%)
Regression	Complete Regression	22 (50 %)
	Partial Regression	22 (50 %)
	1:4	4 (18, 2 %)
	2:4	15 (68, 2 %)
	3:4	3 (13, 6 %)
Localization	Distal	26 (59, 1 %)
	Middle	16 (36, 4 %)
	Proximal	2 (4, 5 %)
Primary Tumor Volume (cm ³)	Mean±Std	33, 81±31, 91

Table 2. Signal intensity and tumor volume changes before and after CRT for all patients.

Parameters	Before	After	P
Tumor Volume (cm ³)	33, 81	5, 81	<0.001*
Signal Intensity of T2WI	3, 5±1, 2	2, 1±0, 8	<0, 001*
ADC (x10 ⁻⁶ mm ² /sec)	911±186	1374±283	<0, 001*
Skewness of T2WI	0, 08	0, 34	0, 004*
Skewness of ADC	0, 20	0, 15	0, 339
Kurtosis of T2WI	-0.20	-0, 13	0, 903
Kurtosis of ADC	-0.34	-0.53	0, 313

* Wilcoxon Rank Sum Test was used for first order textural feature comparison before and after neoadjuvant CRT, * p<0, 05.

Table 3. Comparison of parameters between complete responders and partial responders.

-	-	Complete Responder	Partial Responder	P
Localization	Distal	14 (63, 6 %)	12 (54, 5 %)	^a 0, 550
	Middle	8 (36, 4 %)	8 (36, 4 %)	
	Proximal	0 (0 %)	2 (9, 1 %)	
Age	Mean±Std	55, 86±11, 81	57, 18±10, 34	^b 0, 588
Primary Tumor Volume (cm ³)	Mean±Std	17, 07±11, 32	50, 55±37, 01	^b <0, 001*
Tumor Volume Changes (cm ³)	Mean±Std	17, 07±11, 32	38, 92±33, 84	^b 0, 011*
Pre-CRT ADC (x10 ⁻⁶ mm ² /sec)	Mean±Std	924, 14±169, 34	898, 15±205, 65	^c 0, 650
Post-CRT ADC (x10 ⁻⁶ mm ² /sec)	Mean±Std	1496, 27±285, 61	1251, 15±226, 57	^c 0, 003*
ADC Changes (x 10 ⁻⁶ mm ² /sec)	Mean±Std	572, 1±264, 4	353±170, 6	^b 0.002*
Pre-CRT Signal intensity of rT2WI	Mean±Std	3, 55±1, 28	3, 51±1, 20	^b 0, 771
Post-CRT Signal Intensity of rT2WI	Mean±Std	1, 81±0, 60	2, 52±0, 99	^b 0, 006*
rT2WI Changes	Mean±Std	-1, 74±1, 31	-0, 99±1, 40	^b 0, 058

^aFisher Freeman Halton Test, ^bMann Whitney U Test, ^c Student t Test, *p<0, 05, rT2WI: relative signal intensity of T2WI.

Table 4. Textural feature before and after CRT for partial and complete responders.

Partial Responders				
Parameters	-	Before	After	P
Skewness of T2WI	Mean±Std	0, 20±0, 41	0, 25±0, 30	0, 482
Kurtosis of T2WI	Mean±Std	-0, 14±0, 68	-0, 35±0, 57	0, 128
Skewness of ADC	Mean±Std	0, 26±0, 49	0, 12±0, 54	0, 247
Kurtosis of ADC	Mean±Std	-0, 25±0, 70	-0, 44±0, 84	0, 353
Complete Responders				
Skewness of T2WI	Mean±Std	-0, 03±0, 48	0, 44±0, 54	0, 001*
Kurtosis of T2WI	Mean±Std	-0, 26±0, 79	0, 08±1, 14	0, 112
Skewness of ADC	Mean±Std	0, 14±0, 62	0, 18±0, 48	0, 848
Kurtosis of ADC	Mean±Std	-0, 43±1, 07	-0, 61±0, 64	0, 924

Wilcoxon Rank Sum Test was used for first order textural feature comparison before and after neoadjuvant CRT, * p<0, 05

were not significantly different before and after neoadjuvant CRT in either group ($P > 0.05$) (Table 4).

4. DISCUSSION

This study aimed to investigate whether first-order textural features derived from T2-WI and ADC maps could predict the complete response of locally advanced rectal cancer to neoadjuvant CRT. The results indicated that the skewness of T2-W images of primary tumors and lesions after treatment were statistically different in the complete response group compared to the incomplete response group. This was associated with a pathologic complete response for locally advanced rectal cancer. Decreased relative T2-WI signal intensity was also a good indicator for the complete response group after neoadjuvant CRT. Furthermore, ADC values and tumor volume changes were related to complete response in locally advanced rectal cancer. In addition, within this dataset, the absolute ADC value (mean ADC value = $1310.02 \times 10^{-6} \text{ mm}^2/\text{s}$ with accuracy values of 78.1%) could be used as a marker for a complete response after the completion of neoadjuvant CRT for locally advanced rectal cancer. However, kurtosis derived from the ADC maps and T2-W images did not play a role in predicting the complete response to neoadjuvant CRT of locally advanced rectal cancer.

The differentiation of residual tumors from fibrosis after neoadjuvant CRT for locally advanced rectal cancer using MRI is a challenging task for radiologists. Finding reliable non-invasive markers of pathologic response to neoadjuvant CRT is becoming increasingly important due to the non-operative management of locally advanced rectal cancer. Texture analysis of MRI has been recommended as a promising technique for the detection of intra-tumor heterogeneity attributed to various factors, such as hypoxia, necrosis, angiogenesis, and fibrosis, potentially related to pathologic tumor response to neoadjuvant CRT [26, 31]. Various studies on locally advanced rectal cancer have looked into the value of T2-WI beyond visual image

evaluation [26, 30, 32-35]. Aker *et al.* showed that skewness of T2-W images after the completion of neoadjuvant CRT could differentiate complete responders from partial responders with $P < 0.001$ [30]. However, our results did not support these findings: in our study, the skewness derived from the T2-W images before and after neoadjuvant CRT was statistically different in the complete response group ($P = 0.001$) compared to the partial response group ($P = 0.482$). The positive change in the skewness of the complete response group of this study's dataset showed a significant leftward shift of the signal intensity curve. This suggested that the relative T2-WI signal intensity homogeneously decreased in favor of fibrosis after neoadjuvant CRT, indicating a complete response in the tumor [34]. Skewness is a measure of the asymmetry of the distribution of a signal intensity curve within an ROI. The wide distribution of the T2-WI signal intensities in the primary tumor can be attributed to the heterogeneity of the tumor cell population, tumor stroma component, vascularization, and blood flow [36, 37]. These heterogeneous profiles changed to more homogeneous profiles after neoadjuvant CRT. The changes in the skewness of the T2-W images in the partial response group were insignificant in our study due to the incomplete conversion of the tumors to fibrosis. A study conducted by Kluza *et al.* showed statistically significant T2-WI signal intensity changes in complete responders compared to partial responders, with 82% accuracy [34]. However, in the current study, relative T2-WI signal intensity changes failed to define the complete response group, whereas relative T2-WI signal intensity after neoadjuvant CRT distinguished a complete response. De Cecco *et al.* conducted two studies on the textural features of T2-WI in locally advanced rectal cancer. In one study of 15 consecutive patients, they showed that only the kurtosis of primary tumors and mid-treatment images were significantly different in complete responders compared to all patients, with $P = 0.010$ and $P = 0.045$, respectively. In a study of 12 consecutive patients, they found that pre-treatment kurtosis was significantly different among com-

plete and partial responders, with $P = 0.01$ [26, 32]. Our kurtosis findings did not support this; however, the main limitation of De Cecco *et al.*'s study was that the cohort included a small group of patients, so the P values are questionable, and they were not corrected by post hoc analysis. Shu *et al.* aimed to identify multiple first-order textural parameters derived from T2-WI as potential biomarkers of therapy responses in locally advanced rectal cancer. They found that the skewness, entropy, and energy of primary tumors significantly differed from responders and non-responders, with up to a 91.67% specificity, but they could not show any significant difference after neoadjuvant CRT [33]. Crimi *et al.* did not find a significant difference in textural features derived from T2-W images for the prediction of the complete response of locally advanced rectal cancer to neoadjuvant CRT [35].

The current study also indicated that the quantitative analysis of DWI shows promising results for the prediction of complete response to the neoadjuvant CRT of locally advanced rectal cancer. We found that a cut-off value of $1310 \times 10^{-6} \text{ mm}^2/\text{s}$ predicted a complete response with a sensitivity of 72.73% and a specificity of 77.27%, which was in line with previous studies. Several studies have proposed cut-off ADC values for complete response in the range of $1200\text{--}1350 \times 10^{-6} \text{ mm}^2/\text{s}$ [38-40]. In contrast, in a meta-analysis of 10 prospective and 8 retrospective studies, the mean ADC values for complete and partial response after neoadjuvant CRT were $1510 \times 10^{-6} \text{ mm}^2/\text{s}$ and $1290 \times 10^{-6} \text{ mm}^2/\text{s}$, respectively [41]. Many studies have attempted to calculate the optimal cut-off value, but these values were inconsistent; therefore, an absolute ADC cut-off value alone cannot reliably distinguish residual viable tumor cells from post-treatment fibrosis. However, the meta-analysis showed that changes in the ADC before and after neoadjuvant CRT showed higher sensitivity and specificity than post-CRT ADC measurements alone [41]. This finding was also supported by our study: a statistically significant difference was found between the partial and complete pathologic response groups using change in the absolute ADC. We also found that primary tumor volume and tumor volume changes after neoadjuvant CRT were significantly different between the complete and partial response groups, with $P < 0.001$ for primary tumor volume and $P = 0.011$ for tumor volume changes. However, we did not find a significant relationship between tumor volume and histopathologic tumor regression grade, as was reported in previous studies [42]. Although many studies have evaluated the relationship between tumor volume change and tumor response to neoadjuvant CRT, the results have been inconsistent [25, 43, 44].

Our study has some limitations. First, our study enrolled a small group of patients, so these findings should be confirmed by further research using a large dataset. Second, we did not perform volumetric texture analysis; instead, our study was based on a manually drawn ROI, which may have been observer dependent. Blazic *et al.* have shown that the choice of ROI placement method significantly affects the measurement of ADC values, and volumetric texture analysis provides the best accuracy for evaluating treatment response [45]. Finally, our study was retrospective, thus allowing for bias in the patient selection.

CONCLUSION

Relative T2-WI signal intensity and ADC values were significantly statistically different in the complete response group after neoadjuvant CRT compared to the partial response group. The statistically different skewness of the T2-WI in the complete response group before and after CRT indicated that the signal intensity values of all the voxels shifted homogeneously to the left of the graph. This was attributed to the tumor cells in all the voxels having fully responded to the neoadjuvant CRT and converted into fibrosis. Conversion to fibrosis was also supported by changes to ADC values. In addition, the ADC cut-off value of $1310 \times 10^{-6} \text{ mm}^2/\text{s}$ predicted a complete response, with a sensitivity of 72.73%, a specificity of 77.27%, and an accuracy of 78.1%. We have shown that ADC maps can be used as predictors of complete response after the completion of neoadjuvant CRT for locally advanced rectal cancer.

ORIGINAL RESEARCH

The preliminary result of this study was presented as an oral presentation at European Society of Gastrointestinal Abdominal Radiology (ESGAR) Annual Meeting 2020, (Virtual conference).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research procedure was approved by the Institutional Review Board of Istanbul Faculty of Medicine at Istanbul University Turkey, (Approval No:2019/659).

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The study on humans was conducted in accordance with the ethical rules of the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

This is retrospective study, requirement to obtain written informed consent was waived.

STANDARDS OF REPORTING

STROBE guidelines were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding authors, [M.G.K.], upon reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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