# Apparent diffusion coefficient histogram analysis for predicting neoadjuvant chemoradiotherapy response in patients with rectal cancer

Andelib Babatürk
Ayşe Erden
İbrahim Ethem Geçim

**PURPOSE**
This study aimed to retrospectively evaluate the apparent diffusion coefficient (ADC) histograms in predicting chemoradiotherapy (CRT) response in patients with locally advanced rectal cancer (LARC).

**METHODS**
A total of 51 patients who underwent surgery in our institution for rectal cancer following neoadjuvant CRT between November 2013 and July 2019 were enrolled. Conventional magnetic resonance (MR) and diffusion-weighted images obtained before and after CRT were evaluated retrospectively. All tumor-containing regions of interests were drawn in 3 selected axial images, and special software for histogram analysis was used to evaluate ADC distribution. ADC cutoff values from post-CRT ADC histogram were calculated from receiver operating characteristic (ROC) analysis for evaluating CRT response.

**RESULTS**
In histopathological analysis, 5 patients (9.8%) had minimal response (group 1), 31 patients (60.8%) had partial response (group 2), and 15 patients (29.4%) had complete or almost complete response (group 3). In the ADC histogram, minimum, maximum, 10th, 25th, 50th, 75th, and 90th percentile, mean ADC values, and skewness values of groups 2 and 3 showed significant changes before and after CRT, but no difference was found within group 1 values. The mean, 25th, 50th, 75th percent ADC values after CRT and skewness, and kurtosis values were significantly different between group 1 and group 3. Skewness value from the ADC histogram in post-CRT magnetic resonance imaging had the best diagnostic performance with an area under the ROC curve of 0.851 ($P = .003$) for detecting group 3. The skewness cutoff calculated from the ROC analysis was 0.210 for evaluating CRT response. The sensitivity and specificity of the cut-off value were 100% and 61.4%, respectively.

**CONCLUSION**
The ADC histogram analysis seems to have potential application in predicting response to neoadjuvant CRT in patients with locally advanced rectal cancer.

From the Radiology Unit (A.B. ✉ dr.andelib@ gmail.com), Akçakoca State Hospital, Akçakoca, Düzce, Turkey; Department of Radiology (A.E.), and Department of General Surgery (E.G.), Ankara University, School of Medicine, Ankara, Turkey.

Colorectal cancer is among the most important causes of cancer-related deaths worldwide.[1] In the last few decades, the advanced surgical methods and neoadjuvant chemoradiotherapy (CRT) implementations have been shown to be useful in significantly reducing the local recurrence rates in locally advanced (stages T3-4 or node-positive tumor) rectal cancer. Neoadjuvant CRT not only can reduce the recurrence but also can downstage the tumor and increase the tumor resection and sphincter-preserving surgery rates.[2-6]

An accurate evaluation of response to neoadjuvant CRT is crucial because of its major effect on patient management. Although highly valuable in evaluating the primary tumor and its extension to the mesorectal fascia, conventional magnetic resonance imaging (MRI) has some limitations in distinguishing the residual tumor from post-treatment fibrosis.[5] Diffusion-weighted imaging (DWI), on the other hand, is a non-invasive functional MRI technique and is sensitive to the motion of water molecules in biological tissues. It has high specificity in reflecting tissue cellularity, distinguishing post-treatment recurrence

or residual tumor tissue from fibrosis or necrosis.[6-9] Apparent diffusion coefficient (ADC) mapping is thought to contribute to predicting prognosis and response to neoadjuvant CRT.[5,6,10,11] However, CRT-applied tumor tissue has a very heterogeneous microstructure composed of residual (viable) tumor cells, necrosis, fibrosis, and mucous substance. In addition, studies have shown the success of ADC values in determining tumor aggression in colon cancer.[12]

Literature data show that parameters derived from ADC histogram curves reflect tissue heterogeneity more precisely than mean ADC values.[10-15] Histogram analysis which is a new approach to ADC measure is based on pixel distribution and can be used as a quantitative marker of the biological heterogeneity of the tumor. A spectrum of ADC values, such as minimum ADC, mean ADC, maximum ADC, various ADC percentiles, as well as statistical parameters, which consider the extremes of the data set rather than focusing solely on the average, like skewness and kurtosis can be estimated by using this method. In tumor restaging, changes in parameters of histogram analysis, compared to pre-CRT data, provide information about the microstructural heterogeneity of the tumor response.[10,11] By applying histogram analysis to pre- and post-CRT images, the change in the microstructure of the tumor can be graphically visualized and quantified with descriptive parameters derived from the ADC histogram.[13,14]

The purpose of our study is to assess the effectiveness of ADC histogram analysis parameters in predicting response in rectal cancer patients who underwent neoadjuvant CRT.

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**Main points**

- In response to the chemoradiotherapy (CRT), a leftward skew of the histogram curve (negative skew), a decrease in the height of the histogram peak (negative kurtosis), and an increase in apparent diffusion coefficient values are observed.

- Apparent diffusion coefficient histogram analysis seems to have potential application in predicting complete response to preoperative CRT in patients with locally advanced rectal cancer.

- The post-CRT skewness value of 0.210 is highly sensitive in determining the response to neoadjuvant CRT.

## Methods

The study protocol was approved by the institutional medical ethics committee of our hospital (decision number 04-230-18, dated February 26, 2018), and written informed consent was waived for this retrospective study.

### Patients

Data were collected from our picture archiving and communication system in consecutive patients with rectal cancer. A total of 274 patients who were diagnosed with non-mucinous rectal adenocarcinoma by colonoscopic biopsy and underwent pelvic MRI in our radiology department between November 2013 and July 2019 were retrospectively evaluated. Mucinous adenocarcinomas were excluded in the initial assessment since ADC values of mucinous subtypes are considerably higher than that of non-mucinous carcinomas due to abundant mucin and low cellularity.[16] After CRT, the necrosis of the viable malign cells of mucinous tumor results in a featureless fluid-like signal on the ADC map, and pre- and post-CRT ADCs can overlap.

Thereby, inclusion criteria consisted of histopathologically proven non-mucinous rectal adenocarcinoma, availability of a pretreatment local staging (pre-CRT) MRI, tumor stage higher than T2, long course neoadjuvant therapy, restaging (post-CRT) MRI, and data on the final response of treatment (based on histopathologic results obtained from the surgical specimen).

The following patients did not meet the inclusion criteria for this study and were therefore excluded from the study: (a) 68 patients had no primary staging MRI examination, (b) 103 patients had no restaging MRI, (c) 50 patients had not received the surgery or had surgery in another center, and (d) one patient had post-CRT MRI with low diagnostic quality. A final total study population of 51 patients remained.

The neoadjuvant treatment regime used in patients who were evaluated in the first years consisted of radiation to an average total dose of 45 Gy, divided into 5 days per week, a 28-day treatment period, and one boost of 5.4 Gy. This regimen was applied simultaneously with 5-fluorouracil (5-FU) at a dose of 350 mg/m²/day in the first and fifth weeks of radiation therapy. For the last 5 years, 5-FU infusion and radiation therapy were replaced by preoperative concurrent CRT (45 Gy/25 fractions over 5 weeks and on radiotherapy days 825 mg/m² oral capecitabine twice daily), again followed by a boost of 5.4 Gy. Magnetic resonance imaging scans were performed after completion of CRT at an interval of 6-7 weeks, and surgery was undertaken at 8-9 weeks after CRT. The tumor regression grading (TRG) system proposed by Dworak[17] was used for histopathological response assessment.

### Patient preparation

In order not to stimulate intestinal peristalsis, a pelvic MRI was performed after at least 5-6 hours of fasting. Before the examination, bowel cleansing and antiperistaltic medication were not applied. No air, fluid, or rectal gel was administrated to achieve rectum distension.

### MRI protocol

Magnetic resonance imaging examinations were performed with standard body matrix coil on a 3 Tesla imaging system (MAGNETOM Verio, Siemens Medical Solutions). Scan protocol used in this study was as follows: sagittal turbo spin-echo (TSE) T2-weighted (slice thickness: 3.5 mm; distance factor [DF]: 15%; repetition time [TR]: 4500 ms; echo time [TE]: 104 ms; echo trains per slice: 13; field-of-view [FOV]: 220 mm; flip angle [FA]: 120°; matrix: 384 × 307; number of signal averages [NSA]: 2; acquisition time: 4.05 minutes); axial TSE T2-weighted (slice thickness: 5.0 mm; DF: 20%; TR: 5450 ms; TE: 93 ms; echo trains per slice: 8; FA: 150°; FOV: 220 mm; matrix: 320 × 256; NSA: 3; acquisition time: 2.18 minutes); oblique axial high resolution (HR) TSE T2-weighted (slice thickness: 3.0 mm; DF: 16%; TR: 5460 ms; TE: 58 ms; echo trains per slice: 12; FA: 145°; FOV: 220 mm; matrix: 320 × 256; NSA: 4; acquisition time: 4:54 minutes); oblique coronal HR TSE T2-weighted (slice thickness: 3.0 mm; DF: 16%; TR: 5180 ms; TE: 58 ms; echo trains per slice: 15; FA: 135°; FOV: 220 mm; matrix: 320 × 256; NSA: 4; acquisition time: 6:00 minutes); oblique axial HR TSE contrast-enhanced fat suppressed T1-weighted (slice thickness: 3.5 mm; DF: 14%; TR: 495 ms; TE: 12 ms; echo trains per slice: 39; FA: 140°; FOV: 180 mm; matrix: 320 × 256; NSA: 3; acquisition time: 4:31 minutes); and oblique and coronal HR TSE contrast-enhanced fat suppressed T1-weighted images (DF: 14%; slice thickness: 3.5 mm; TR: 495 ms; TE: 12 ms; echo trains per slice: 39; FA: 140°; FOV: 180 mm;

matrix: 320 × 256; NSA: 2; acquisition time: 3:35 minutes). The sagittal images were used for planning oblique axial and oblique coronal images, respectively, perpendicular and parallel to the long axis of the rectal tumor.

Axial-free breathing DWI was performed with 3 different b values (50, 400, and 1000 s/mm$^2$) with a single-shot echo-planar imaging sequence and spectral attenuated inversion-recovery fat-suppression technique. Diffusion-weighted imaging parameters were as follows: slice thickness: 5.0 mm; DF: 30%; TR: 646 ms; TE: 11 ms; echo trains per slice: 47; FA: 140°; FOV: 180 mm; matrix: 320 × 288; NSA: 2; acquisition time: 3:06 minutes. Parallel imaging with a reduction factor of 2 was used in all sequences. The operating system automatically generated the apparent diffusion coefficient maps in the grayscale using a monoexponential decay model containing all 3 b values.

### Image evaluation

Magnetic resonance images were transferred to the workstation (Syngo.via, Siemens Healthineers) and evaluated retrospectively. Measurements were made by a single observer, blinded to the patients' clinical information and histopathology results. Since diffusion-weighted images have higher resolution than ADC maps, regions of interests (ROIs) were drawn to include the entire tumor from 3 different diffusion-weighted images, where the tumor is the largest and best seen in the axial plane. Later, these ROIs were copied to the ADC map. Special software (Syngo.via Oncology, Siemens Healthineers) was used for the ROI-based ADC histogram analysis. Minimum, mean, maximum ADC values, 10th, 25th, 50th, 75th, 90th percentiles, and skewness (asymmetry characterized by a right or left shift in the normal distribution curve) and kurtosis (a measure that describes the shape of a distribution's tails in relation to its overall shape) values were derived from ADC histograms. For each parameter, 3 measurements were averaged. The following equation was used to calculate the ADC change (ΔADC) between the groups before and after CRT: [(post-CRT ADC − pre-CRT ADC)/pre-CRT ADC] × 100.

### Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences Version 23 program (IBM corp.).

The compatibility of the quantitative data to normal distribution was tested by Shapiro–Wilk test and graphical analysis. Analysis of variance test was used to check whether the means of the 3 groups were significantly different from each other. The Student t-test was used for comparisons of normally distributed quantitative variables between 2 groups, and Mann–Whitney U test was used for comparisons of quantitative variables that did not show normal distribution between 2 groups. Paired samples t test was used for evaluating normally distributed variables before and after treatment. In the comparison of qualitative data, Pearson chi-square test, Fisher Freeman Halton test, and Fisher exact test were used. Receiver operator characteristics (ROC) analysis was used to determine the cutoff value according to the regression grade of the tumor. A P value less than .05 was considered indicative of a statistically significant difference.

## Results

In this study, a total of 51 patients (13 women and 38 men) were included. The mean age of the patients was 59.2 years (age range: 20-85 years). Other demographic features are shown in Table 1. On histopathological response assessment, 5 patients (9.8%) had TRG 1 (minimal response), 31 patients (60.8%) had TRG 2 (partial response), 8 patients (15.6%) had TRG 3 (almost complete response), and 7 patients had (13.7%) TRG 4 (complete response). Since there was a heterogeneous distribution in numbers, TRG 3 and 4 were combined and the patients were analyzed under 3 groups as follows: patients with minimal response (group 1), partial response (group 2), and complete/almost complete response (group 3). Pre- and post-CRT minimum, maximum, mean ADC values, 10th, 25th, 50th, 75th, and 90th percentiles were calculated from the ADC histogram analysis, and the skewness and kurtosis values are shown in Table 2.

The mean ± standard deviation (SD) pre-CRT tumor ADC$_{mean}$ value was 1.02 × 10$^{-3}$ mm$^2$/s ± 0.19, whereas the mean ± SD post-CRT ADC$_{mean}$ was 1.35 × 10$^{-3}$ mm$^2$/s ± 0.35. Considering all patients, the mean ADC$_{mean}$ value increased significantly after CRT. However, when the comparison was made between the groups, it was seen that this significant difference was caused by the groups showing partial

| Table 1. Patient demographics | | |
|---|---|---|
| | n = 51 | % |
| **Primary T staging** | | |
| T1 | 4 | 7.8 |
| T2 | 3 | 5.9 |
| T3 | 32 | 62.7 |
| T4 | 12 | 23.5 |
| **Final T staging** | | |
| ypT0 | 7 | 13.7 |
| ypT1 | 1 | 2.0 |
| ypT2 | 12 | 23.5 |
| ypT3 | 27 | 52.9 |
| ypT4 | 4 | 7.8 |
| **Final N staging** | | |
| Nx | 5 | 9.8 |
| N0 | 35 | 68.6 |
| N1a | 3 | 5.9 |
| N1b | 2 | 3.9 |
| N1c | 2 | 3.9 |
| N2a | 0 | 0.0 |
| N2b | 4 | 7.8 |
| **Mesorectal fascia involvement** | | |
| Present | 16 | 31.4 |
| Absent | 26 | 51.0 |
| Suspicious | 9 | 17.6 |
| **Extramural venous invasion** | | |
| Present | 10 | 19.6 |
| Absent | 41 | 80.4 |

response and the groups showing complete/almost complete response. There was no significant difference in any ADC measurements, including the mean ADC$_{mean}$ values before and after CRT in patients with minimal response.

Significant changes were observed before and after CRT in the skewness, minimum, 10th, 25th, 50th, 75th, and 90th percentile, mean and maximum values in groups 2 and 3 ($P < .05$) (Figure 1). However, no significant difference was found between pre- and post-CRT values of group 1 (Figure 2). Post-CRT mean, minimum, 10th, 25th, 50th, 75th, and 90th percentile, skewness and kurtosis values were significantly different ($P < .05$) between group 1 and group 3 (Table 3). There was no significant difference in the groups regarding the maximum ADC values. There was no statistical difference between patients with partial response (group 2) and group 1 or group 3 in terms of histogram ADC values.

**Table 2.** Pre- and post-CRT minimum, maximum, mean ± SD of ADC histogram analysis parameters, and skewness and kurtosis values

| | Pre-CRT | | | Post-CRT | | |
|---|---|---|---|---|---|---|
| | Minimum | Maximum | Mean ± SD | Minimum | Maximum | Mean ± SD |
| Minimum | 0.14 | 1.07 | 0.57 ± 0.18 | 0.19 | 1.77 | 0.87 ± 0.37 |
| 10th percentile | 0.47 | 1.35 | 0.76 ± 0.15 | 0.57 | 1.99 | 1.05 ± 0.34 |
| 25th percentile | 0.56 | 1.55 | 0.86 ± 0.17 | 0.61 | 2.14 | 1.16 ± 0.34 |
| 50th percentile | 0.69 | 1.77 | 0.99 ± 0.19 | 0.68 | 2.37 | 1.34 ± 0.35 |
| 75th percentile | 0.84 | 1.99 | 1.14 ± 0.22 | 0.77 | 2.48 | 1.51 ± 0.37 |
| 90th percentile | 0.97 | 2.12 | 1.31 ± 0.24 | 0.87 | 2.56 | 1.66 ± 0.37 |
| Maximum | 1.18 | 2.35 | 1.67 ± 0.29 | 0.95 | 2.88 | 1.92 ± 0.39 |
| Mean | 0.72 | 1.76 | 1.02 ± 0.19 | 0.70 | 2.31 | 1.35 ± 0.35 |
| Kurtosis | −0.91 | 2.82 | 0.72 ± 0.82 | −1.20 | 2.95 | 0.22 ± 0.83 |
| Skewness | −0.31 | 1.51 | 0.61 ± 0.40 | −0.82 | 1.52 | 0.25 ± 0.48 |

ADC values are given in units of $10^{-3}$ mm²/s.
CRT, chemoradiotherapy; SD, standard deviation; ADC, apparent diffusion coefficient.

In 4 patients, post-CRT ADC values showed an unexpected decrease in the histogram analysis. In 2 of these 4 patients whose histograms were right-skewed, in the histopathologic examination of the resected specimens, there were no residual tumor cells (pathological complete response).

The post-CRT skewness value derived from the ADC histogram had the best diagnostic performance with an area of 0.851 ($P$ =.003) under the ROC curve to identify patients with complete response (Table 4). To evaluate the CRT response, the cutoff skewness value calculated from the ROC analysis was determined as 0.210 with 100% sensitivity (95% CI: 56-100) and 61.4% specificity (95% CI: 46-75) (Figure 3).

Patients with minimal response to treatment can be identified with the aid of ADC histogram analysis. The 75th percentile ADC values had the best diagnostic performance for discrimination group 1 (Table 4). From the ROC analysis, the limit

75th percentile ADC values were calculated as 1.35 × $10^{-3}$ mm²/s with 100% (95% CI:54-82) sensitivity and 70% (95% CI: 46-100) specificity.

There was a significant difference in ADC change (ΔADC) before and after CRT between the minimally responsive group and the group with complete/almost complete response ($P$ = .04).

## Discussion

In this single-center, retrospective ADC histogram analysis study, a leftward skew of the histogram curve (negative skew), a decrease in the height of the histogram peak (negative kurtosis), and an increase in ADC values are observed in response to the CRT. The post-CRT skewness value derived from the ADC histogram is highly sensitive in identifying patients with complete response. The 75th percentile ADC values had the best diagnostic performance for determining the patients with minimal response to treatment.

In locally advanced rectal cancer cases, neoadjuvant CRT before operative treatment provides higher rates of sphincter-sparing surgery, less-frequent anastomotic stenosis, and better local control than adjuvant regimens, while the long-term survival rates of both approaches are similar.[18] The neoadjuvant regimen can also eradicate
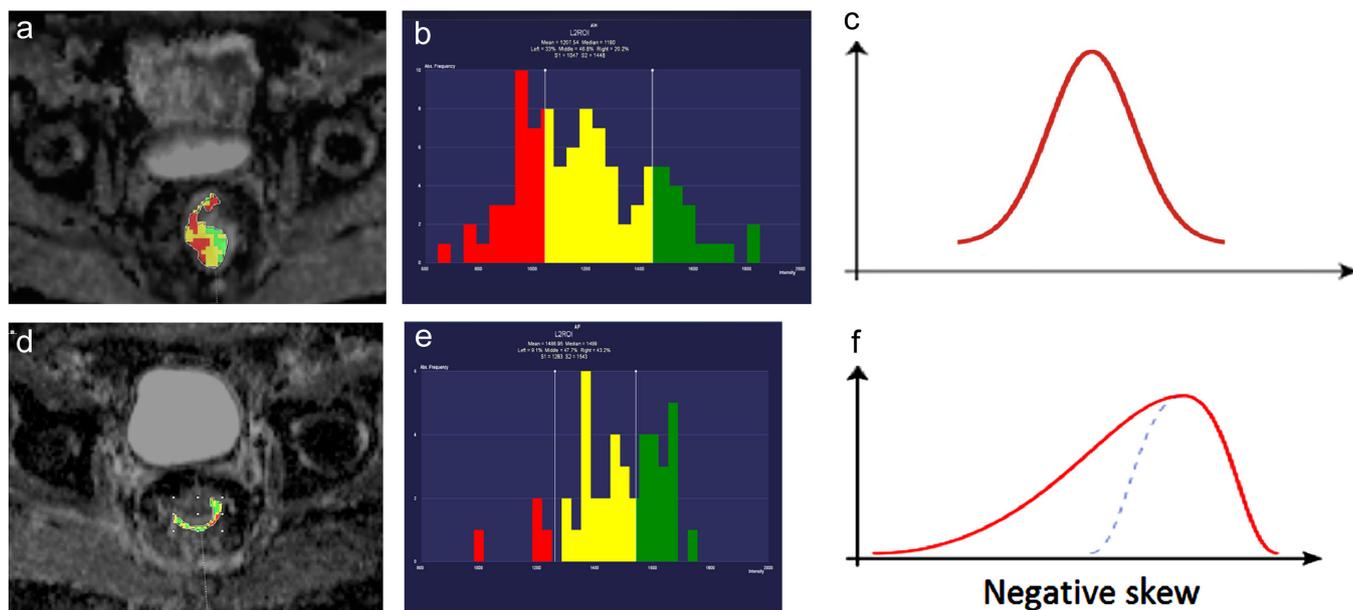


**Figure 1. a-f.** Histogram analysis in 62-year-old man with complete response following neoadjuvant CRT for rectal cancer. Pre-CRT color-coded ADC map **(a)** and ADC histogram **(b)**. Mean Pre-CRT ADC is 1.20. Color-code red voxels, ADC values < 1.050 × $10^{-3}$ mm²/s; yellow voxels 1.050-1.450 × $10^{-3}$ mm²/s; green voxels > 1.450 × $10^{-3}$ mm²/s. The normal distribution curve **(c)**. Post-CRT color-coded ADC map **(d)**. Left-skewed histogram curve after CRT **(e)**: the mass of distribution concentrated on the right indicating an increase in the ADC values of voxels over the time points. Mean post-CRT is 1.45 × $10^{-3}$ mm²/s. Most voxels contain an ADC greater than the mean. The histogram has a flatter tail on the left. Negative skew diagram **(f)**. CRT, chemoradiotherapy; ADC, apparent diffusion coefficient.
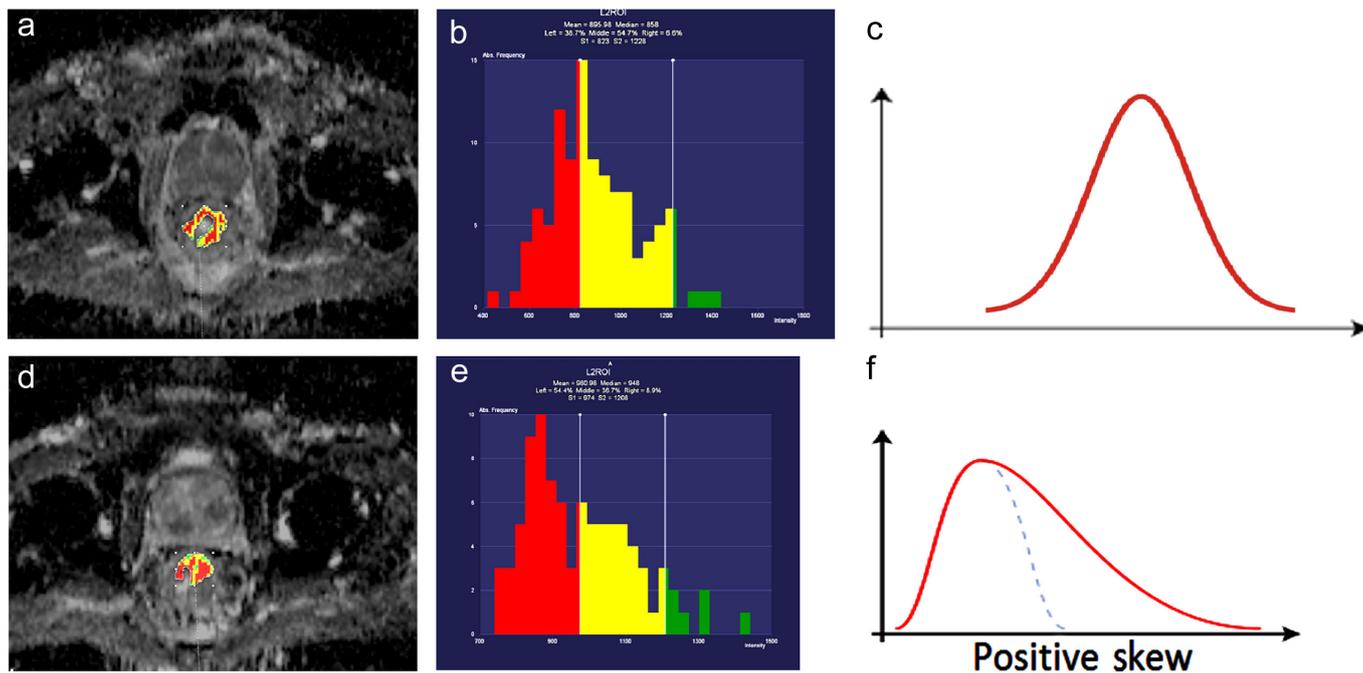
**Figure 2. a-f.** Histogram analysis in 79-year-old man with minimal response following neoadjuvant CRT for rectal cancer. Pre-CRT color-coded ADC map (**a**) and ADC histogram (**b**). The normal distribution curve (**c**). Post-CRT color-coded ADC map (**d**) and ADC histogram (**e**). After CRT, ADC changed from 0.9 to $1.0 \times 10^{-3}$ mm$^2$/s. The post-CRT ADC histogram demonstrates positive skewness. Most of the voxels are concentrated on the left of the graphic and contain ADC values less than the mean. The tail on the right side of the distribution is longer and flatter. The positive skew diagram (**f**).

the tumor completely (complete response). In recent years, the opinion has come to the fore that selected patients who achieve a clinical complete response after neoadjuvant CRT can be followed up without surgery (watch-and-wait approach).[19,20] For this reason, predicting the response to CRT is very important in terms of the treatment strategy.

Various studies have shown that MRI is quite successful in predicting the response to treatment.[21,22] In a meta-analysis, it was found that MRI has 78%

sensitivity and 81% specificity in predicting the response of tumor after preoperative treatment.[22] Diffusion-weighted imaging can be added to the protocol to improve the diagnostic performance of MRI in restaging after CRT.[5,6,11] In a study (involving 21 patients) conducted by Napoletano et al.,[23] the sensitivity of conventional MRI is 80% and the specificity is 50% in response evaluation. In this study,

the addition of DWI to the conventional MRI increased the sensitivity to 100% and the specificity to 67%, thereby improving the morphologic information provided by conventional examination. Visual assessment of signal changes on DWI and measurements from ADC map derived from DWI can differentiate post-treatment recurrence or residual tumor tissue from post-treatment changes or necrosis.[5,6,10,11] However,

**Table 3.** Changes with respect to treatment response in ADC histogram data in groups 1 and 3

|  | Differences in mean values | P |
|---|---|---|
| Mean | −464.78 | .023 |
| Minimum | −458.74 | .040 |
| 10th percentile | −407.87 | .047 |
| 25th percentile | −458.07 | .023 |
| 50th percentile | −495.00 | .015 |
| 75th percentile | −510.43 | .021 |
| 90th percentile | −449.14 | .047 |
| Maximum | −311.08 | .276 |
| Kurtosis | 1.12 | .023 |
| Skewness | −0.66 | .020 |

ADC, apparent diffusion coefficient.

**Table 4.** Diagnostic performances of post-CRT ADC values and kurtosis and skewness in determining patients with complete response and minimal response

|  | Complete response | | Minimal response | |
|---|---|---|---|---|
|  | AUC | P | AUC | P |
| Minimum | .724 | .059 | .852 | .010 |
| 10th percentile | .718 | .067 | .774 | .046 |
| 25th percentile | .763 | .027 | .826 | .018 |
| 50th percentile | .766 | .025 | .835 | .015 |
| 75th percentile | .737 | .046 | .865 | .008** |
| 90th percentile | .685 | .119 | .835 | .015 |
| Maximum | .640 | .239 | .700 | .145 |
| Mean | .744 | .040 | .843 | .012 |
| Kurtosis | .601 | .396 | .826 | .018 |
| Skewness | .851 | .003* | .822 | .019 |

CRT, chemoradiotherapy; ADC, apparent diffusion coefficient; AUC, area under the curve.
*The post-CRT skewness value derived from the ADC histogram had the best diagnostic performance with an area of 0.851 (P = .003).
**The 75th percentile ADC values had the best diagnostic performance for detecting patients with minimal response.
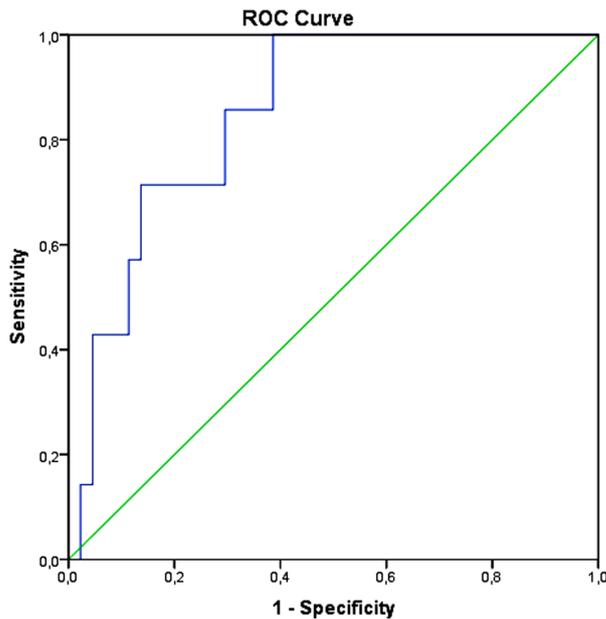
**Figure 3.** ROC curve for skewness as predictor of complete response. ROC, receiver operating characteristic.

according to the literature, data obtained from ADC histogram curves can represent tissue composition more sensitively in comparison to generally used $ADC_{mean}$ values.[10,11,13,14] In tumor ADC measurements, ROI size and positioning significantly affect the measurement results, and small differences may result in non-negligible variations. Particular attention should be paid to ROI size and location to minimize variation among observers. Including the whole tumor volume in the ROI gives the most reproducible result.[24] However, another study showed that ROI size and positioning may affect tumor ADC values, but tumor ADC can be reproducible after CRT if T2-weighted images are available to readers when analyzing post-treatment images.[25]

In our study, histogram parameters showed predictive value in evaluating treatment response. We observed a leftward skewness (negative skewness) in the histogram curve, a decrease in the height of the histogram peak (negative kurtosis), and an increase in ADC values as a response to CRT. Our results were consistent with the findings of the study reported by Enkhbaatar et al.[26] In our study, similar to the literature data, it is observed that the mean post-CRT ADC was significantly higher than pre-CRT ADC. This is presumably due to cell death and reduction of barriers restricting the mobility of water molecules.[23,26,27] In 4 of our patients, ADC values decrease unexpectedly after CRT. In 2 of these 4 patients whose histograms

were right-skewed, in the histopathologic examination of the resected specimens, there were no residual tumor cells (pathological complete response). A similar situation was observed in other studies, and this observation was attributed to the increase in interstitial fibrosis, resulting in less extracellular space for the motion of water molecules. Besides the increased connective tissue production, cytotoxic edema caused by the disruption of cellular membrane depolarization at the end of the treatment can also decrease the ADC values.[26,28,29]

In the literature, the ADC difference has shown higher specificity and sensitivity than the mean ADC values.[30] In our study, a significant difference was found between the group with minimal response and the group with complete/almost complete response in terms of ADC change (ΔADC) before and after CRT.

In the studies in which ADC histogram analysis is used in response assessment, the parameter with the best diagnostic value varies. In the study reported by Choi et al.[14] a significant difference in minimum, mean ADC, 10th, 25th, 50th, and 75th percentile values were found between the complete and incomplete responders. The authors found the 25th percentile value as the parameter showing the best diagnostic performance in determining the patients with complete response. Similarly, in our study, the mean values of 25th, 50th, and 75th percentiles and the kurtosis and skewness values after CRT were significantly

different between group 1 and group 3. However, the skewness value measured from the ADC histogram after treatment had the best diagnostic performance with an AUC of 0.851 to identify patients with complete response. When the cut-off value of skewness was taken as 0.210, the sensitivity of the ADC histogram in evaluating the CRT response was 100% and the specificity was 61.4%.

Our study has some limitations. First of all, our study consists of a small group (n=51). In addition, there is an uneven distribution between the groups in the number of patients. To combine patients with almost complete and complete responses presents a bias. The study was arranged retrospectively and became open to bias in patient selection. Measuring from 3 different slices in the ADC map can be considered among the limitations of our study.

In conclusion, ADC histogram analysis seems to have potential application in predicting complete response to preoperative CRT in patients with locally advanced rectal cancer. The post-CRT skewness value of 0.210 is highly sensitive in determining the response to neoadjuvant CRT. Regarding this issue, however, larger prospective studies are needed to show which histogram parameter and the threshold value are the most useful and significant for assessing treatment response.

### Conflict of interest disclosure

The authors declared no conflicts of interest.

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