The Role of Diffusion MRI in Rectum Cancer Staging and Evaluation of Neoadjuvan Treatment Efficiency

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ABSTRACT

The correct staging of rectal cancer is very important for treatment. This study aims to show the contribution of diffusion-weighted imaging (DWI) to staging, to predict tumor differentiation and neoadjuvant chemoradiotherapy response using DWI. The study consisted of 36 patients and 22 control groups. 12 patients who received neoadjuvant therapy were evaluated before and after treatment. Magnetic Resonance Imaging (MRI) and DWI were performed to all patients and apparent diffusion coefficient (ADC) maps were obtained. The findings were compared with histopathological results. T staging accuracy was 72.2% on MRI. N staging accuracy rate was 75% on the T2 sequence and 72.2% on DWI. Tumoral rectal ADC values were significantly decreased compared to the normal rectal wall ($p< 0.001$). Mean T3 and T4 (extramural) ADC values were significantly decreased compared to the T2 stage (intramural) ADC values ($p< 0.001$). ADC and relative ADC (lymph node / primary tumor ADC) values of the metastatic lymph nodes were significantly decreased compared to benign lymph nodes ($p< 0.001$). According to the ADC cut point, N staging accuracy was found to be 83%. The ADC values of the low differentiated group were significantly decreased compared to the moderately and well-differentiated group ($p< 0.011$). In the control MRI of patients receiving neoadjuvant therapy, the ADC increase in the group that responded well to the treatment was significantly higher than the group with partial response ($p <0.004$). As a result, DWI and ADC are useful for preoperative rectum cancer evaluation.

Keywords: Rectum cancer, Staging, Diffusion MRI

INTRODUCTION

Colorectal cancers are the third most common cancer in men and the second in women.[1] Colorectal cancers account for about 16% of total cancer cases in the world, with 14% in cancer-related deaths.[2] Rectal cancer has a worse prognosis compared to other colon tumors with the rate of metastasis and local recurrence.[3]

The prognosis of rectum cancer is directly related to the stage. Factors determining prognosis; depend on the mural (T1-T2), extramural (T3-T4) spread of the tumor, mesorectal fascia invasion, lymph node spread, and the presence of distant metastasis .[4]

Rectal cancer treatment is determined by local staging. Early-stage tumors (T1, T2, N0) are treated surgically only. Patients with locally advanced rectal cancer (T3, T4, N+) receive neoadjuvant chemoradiotherapy before surgery. Correct tumor staging and appropriate neoadjuvant therapy reduce tumor stage and dramatically reduce local recurrence.[5] In addition, neoadjuvant therapy allows sphincter-sparing surgery and increases prognosis positively.[6] MRI is the best modality in preoperative rectal cancer staging. It also plays a vital role in post-neoadjuvant control assessment and for treatment planning.[7]

DWI is a non-invasive method based on the diffusion of water molecules, showing the biological properties of tissue.[8] ADC (Apparent Diffusion Coefficient) map is created with the relative difference in tissue diffusion and the ADC map allows measurement of ADC values. This quantitative analysis has been shown to be useful for evaluating tumors and distinguishing benign-malignant lesions.[8] Low ADC values reflect cellular density. Recent studies have shown that the ADC value reflects tumor aggressiveness.[9] In addition, intratumoral changes induced by chemoradiotherapy can be calculated.[10]

The aim of this study is to show the contribution of diffusion MRI to staging in patients with rectal cancer, to predict neoadjuvant treatment response and tumor differentiation with diffusion MRI.

PATIENTS AND METHODS

This prospective study was approved by the Ethics Committee. All patients signed a consent form. Between 2015 and 2018, 36 cases who were diagnosed with rectum adenocarcinoma as a result of the colonoscopic biopsy were included in the study. The age range of the cases was 39-87. Only surgical treatment was applied to 24 cases within one month after MRI. Pre-op MRI findings and post-op histopathological findings were compared. 12 patients received preop neoadjuvant therapy and MR images of 12 patients were evaluated before and after neoadjuvant therapy. After the neoadjuvant treatment, MR findings and post-op histopathological findings were compared. Twenty-two patients with normal colonoscopic examination were accepted as the control group. These patients had thick rectum wall on MR

MRI Protocol

1.5 Tesla MRI with 32 channels and the superficial coil was used. Images were obtained in the supine position. In the lower abdomen MRI examination; T2 axial, T2 coronal and sagittal plans, axial T1 and axial T1 dynamic sections were taken.

Spin echo single-shot echo-planar (ss-EPI) sequence was used as DWI. The values of b0, b100 and b600 were used on DWI. ADC maps of all patients were created. In T2 sequence, matrix size was taken as 320 x 224, NEX 2.0, FOV 24 x 24 cm, section thickness 5 mm, inter-sectional space 0.5 mm, TR 7008 ms, TE 109 ms. In DAG sequence, matrix 80 x 128, NEX 4.0, FOV 40 x 40 cm, section thickness 4 mm, TR 5000 and TE 61.9 were taken.

Evaluation of MR Images

MR images were evaluated at the workstation (PHILIPS workstations) without knowing histopathological findings. T, N, and M staging of the tumor was performed according to the AJCC (American Joint Committee on Cancer) TNM staging system with 1.5 Tesla MRI.[11] Staging was done according to the T2 sequence. T staging (mT) of MRI was compared with histopathological T staging (pT). Then, according to histopathological results, ADC measurements were made from T4, T3, T2 stage tumor walls with b600 values of DWI. ADC measurements were made with 5 mm^2 ROI from 3 focuses with the lowest signal. The average of these three ADC values was calculated. 22 control cases with normal rectum walls were also taken ADC measurements. In addition, The mean ADC values of primary tumors with and without lymph node metastasis were compared.

Lymph nodes that bigger than 5 mm, with heterogeneous signal and irregular contours on the T2 weighted image, were accepted pathological. DWI was used as the other method. DWI hyperintense and ADC hypointense, over 5 mm lymph nodes were accepted pathological. According to these two different parameters, if no lymph node was detected, the nodal staging was accepted as N0. 1-3 pathological lymph nodes were evaluated as N1. 4 or more pathological-looking lymph nodes were evaluated as N2. Histopathological N staging was compared with MRI findings. Then, according to the histopathological results, ADC values were measured from the lymph nodes of patients with N0, N1-2. Measurements were made from lymph nodes of at least 5 mm in size. b600 values were used. Relative ADC values of lymph nodes (Lymph Node ADC / Rectum ADC) were calculated and compared. Primary tumor ADC values were compared histopathologically with tumor differentiation grades. In addition, primary tumor ADC

values and tumor volume obtained from pathological specimens were compared.

In patients receiving neoadjuvant therapy, ADC values after and before treatment were subtracted from each other. ΔADC (ADC value after neoadjuvant therapy – ADC value before treatment) was calculated and compared with histopathological tumor regression grading. Histopathological tumor regression grading (TRG) was scored according to the Mandard's system.[12] TRG 1: (complete response), no residual cancer and fibrosis along the wall. TRG 2: rare cancer cells scattered throughout fibrosis. TRG3: increased cancer cells, but still fibrosis dominant TRG4: (minimal response), dominant residual cancer, partial fibrosis. TRG5: (unresponsive), no regression change.

Neoadjuvant Radiotherapy and Chemotherapy

Radiotherapy treatment volume was determined to cover the proximal and distal 3-5 cm distance of the tumor. Perirectal, obturator, internal iliac, external iliac, and presacral lymph nodes were included. Radiotherapy with 18 MV photon energy was applied to this volume with a linear accelerator device in all patients. Pelvic radiation at a total dose of 45 Gy in 25 fractions was applied for 5 days each week for 5 weeks. 800 mg/m^2 capecitabine was administered as a chemotherapeutic agent with radiotherapy.

Statistical Analysis

Numerical measurements was summarized as median and minimum – maximum. The Kolmogorov Smirnov test was used to test whether numerical measurements provide the normal distribution assumption. The Mann Whitney U test was used to compare numerical measurements that did not show normally distribution between the two groups, while the Kruskal Wallis test was used for general comparison between more than two groups. Spearman test was applied for the correlation test. ROC Analysis was performed to determine the appropriate cutting points for the ADC variable. IBM SPSS Statistics 21.0 (SPSS Inc, Chicago, IL, USA) program was used for data analysis. Statistical significance level was taken as $p< 0.05$ in all tests.

RESULTS

Histopathologically, 12 (33%) patients were defined as T2, 12 (33%) patients as T3, and 12 (33%) patients as T4. According to the T2 sequence, 18 of 24 patients who did not receive neoadjuvant therapy were staged correctly (75%). Eight of 12 patients who received neoadjuvant therapy were staged correctly (66%). Totally 26 patients (72.2%) were staged correctly in T staging. 3 cases (8,3%) were staged upper and 7 cases (19,4%) were staged lower. 9 of the 12 T2 stage patients (75%), were correctly staged, 3 of them (25%) were staged upper. 9 of 12 T3 stage patients (75%) were correctly staged, 3 of them (25%) were staged lower (T2). 8 of 12 T4 stage patients (66,6%) were correctly staged and 4 of them (33.3%) were staged as substage (T3) (Table 1a).

Histopathologically, 18 (50%) patients were N0, 9 (25%) patients were N1, 9 patients (25%) were N2. According to the T2 sequence, 19 of 24 patients who did not receive neoadjuvant therapy were staged correctly (79%). 8 of 12 patients who received neoadjuvant therapy were staged correctly (66%). Totally 27 of 36 patients (75%) were staged correctly in N staging. 6 patients (16.6%) were staged upper, 3 patients (8.3%) were staged lower. According to the DWI sequence, 18 of 24 patients who did not receive neoadjuvant therapy were staged correctly (75%). 8 of 12 patients who received neoadjuvant therapy were staged correctly (66%). According to the DWI sequence, a total of 26 patients (72.2%) were staged correctly. 8 patients (22.2%) were staged upper 2 patients (5.5%) were sub-staged (Table 1b).

Rectum ADC Values

The result of statistical analysis for rectum ADC values; when compared with the control group, a statistically significant decrease was observed in the T2 ($p< 0.001$), T3 ($p< 0.001$) and T4 ($p< 0.001$) groups. Compared to the T2 group, a statistically significant decrease was observed in the T3 ($p< 0.001$), and T4 ($p< 0.001$) groups. However, there was no statistically significant difference between the T3 and T4 groups for the rectum ADC values ($p= 0.297$) (Table 1c). In separating rectal cancer and normal rectum wall, the receiver operating

Table 1. Study data and statistical results

a. Comparison of MRI and histopathology findings for T staging

	pT1	pT2	pT3	pT4
mT1	0	0	0	0
mT2	0	9	3	0
mT3	0	3	9	0
mT4	0	0	4	8

b. N staging according to T2 and DAG

	Correct staging	Upper staging	Lower staging
T2	27 (75%)	6 (16.6%)	3 (8.3%)
DAG	26 (72.2%)	8 (22.2%)	2 (5.5%)

c. Median (min-max) values of rectum ADC measurements

	Rectum ADC Values Median (min-max)
CONTROL	1.93 (1.55 - 2.35) $x10^{-3}$
T2	1.38 (1.13 - 1.70)[a] $x10^{-3}$
T3	1.03 (0.76 - 1.29)[ab] $x10^{-3}$
T4	0.95 (0.76 - 1.06)[ab] $x10^{-3}$
p	**< 0.001***

[a] Compared with the control group. [b] Compared with the T2 group. ($p< 0.05$)

d. Rectal cancer ADC values with and without lymph node metastasis

	Rectal cancer ADC Values Median (min-max)
N1-2 Rectal cancer	1.13 (0.76 - 1.70) $x10^{-3}$
N0 Rectal cancer	1.10 (0.77 - 1.46) $x10^{-3}$
p	**= 0.733**

characteristic (ROC) curve was done to evaluate the diagnostic capability of the ADC value. Area under the curve (AUC) was 0.996 (0.930-1.000, $p< 0.001$). The cut point obtained depending on the Youden index was found 1.52 x 10^{-3} mm^2/sec. Sensitivity was 94% and specificity was 100% at this cut-point (Figure 1).

There was no statistically significant difference in ADC values of rectum cancers with and without lymph node metastasis. However, the mean ADC value of the group that did not perform lymph node metastasis was minimally higher ($p= 0.733$) (Table 1d).

Lymph Nodes ADC Values

Histopathologically 18 N0 patients had 18 lymph nodes that 5 mm and above. ADC measurement was performed from these benign lymph nodes. As a result of histopathology, 18 patients with N1-2 had 62 metastatic lymph nodes. ADC was measured from 36 lymph nodes 5 mm and above, most likely to be metastatic. When compared with benign lymph nodes, a statistically significant decrease was observed in the ADC values of metastatic lymph nodes ($p< 0.001$) (Table 2a). In ROC analysis of ADC values of lymph nodes, AUC was 0,928 (0.824 - 0.981, $p< 0.001$). The cut point obtained depending on the Youden index was found 1.33 x 10^{-3} mm^2/sec. Sensitivity was 75% and specificity was 100% at this cut-point (Figure 2a). In lymph node staging with 1.33x10-3 mm^2/sec cut off value, 18 of 18 N0 patients were staged correctly. 12 of 18 N1-2 patients were staged correctly. 6 of them were staged lower. The accuracy rate was 83.3%.

Compared with the relative ADC values of benign lymph node, a statistically significant decrease in metastatic lymph node relative ADC values was observed ($p< 0.001$) (Table 2b). According to ROC analysis of relative ADC values of lymph nodes,

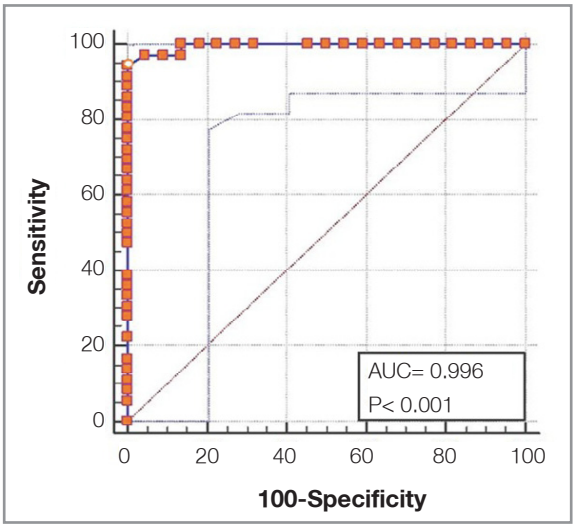

Figure 1. ROC analysis of rectum ADC values

AUC was 0.933 (0.823 - 0.985, p< 0.001). The cut point obtained depending on the Youden index was found 1.47 x 10^{-3} mm^2/sec. Sensitivity is 90.62% and specificity is 88.24% at this cut-point (Figure 2b). In lymph node staging with 1.47 x 10^{-3} mm^2/sec cut off value, 15 of 18 N0 patients were staged correctly. 3 of them were staged upper. 15 of 18 N1-2 patients were staged correctly. 3 of them were staged lower. The accuracy rate was 83.3%.

ADC Values According to Tumor Differentiation Degree

Histopathologically, 4 (11%) patients were poorly differentiated, 26 (72%) patients were moderately differentiated and 6 (17%) patients were well-differentiated. When compared with the poorly differentiated group, a statistically significant increase in ADC values in the moderately differentiated (p< 0.011) and well-differentiated (p< 0.010) group was observed. However, there was no statistically significant difference between moderately differentiated and well differentiated groups (p= 0.069) (Table 2c).

Comparison of ΔADC with Pathological Respons

Tablo 2. Study data and statistical results

a. Lymph Nodes ADC Values	
	Lymph Nodes ADC Values Median (min-max)
Benign lymph nodes	2.11 (1.34-3.25) x10^{-3}
Metastatic lymph nodes	1.17 (0.74-2.00) x10^{-3}
p	< 0.001*
b. Lymph node ADC/ Rectum ADC values	
	Relative ADC Values Median (min-maks)
Benign Relative ADC Values	2.00 (1.21-3.52) x 10^{-3}
Metastatic Relative ADC Values	1.11 (0.60-1.97) x 10^{-3}
p	< 0.001*
c. ADC Values According to Tumor Differentiation Degree	
	Rectal cancer ADC Values Median (min-max)
Poorly differentiated	0.86 (0.76-0.96) x 10^{-3}
Moderately differentiated	1.12 (0.76-1.70)[a] x 10^{-3}
Well differentiated	1.26 (1.08-1.37)[a] x 10^{-3}
p	0.007*
[a] *Compared with poorly differentiated group*	
d. Comparison of ΔADC with Pathological Response	
	ΔADC Median (min-max)
TRG 1-2	0.67 (0.40-0.90) x 10^{-3}
TRG 3-4	0.28 (0.20-0.35) x 10^{-3}
p	0.004*

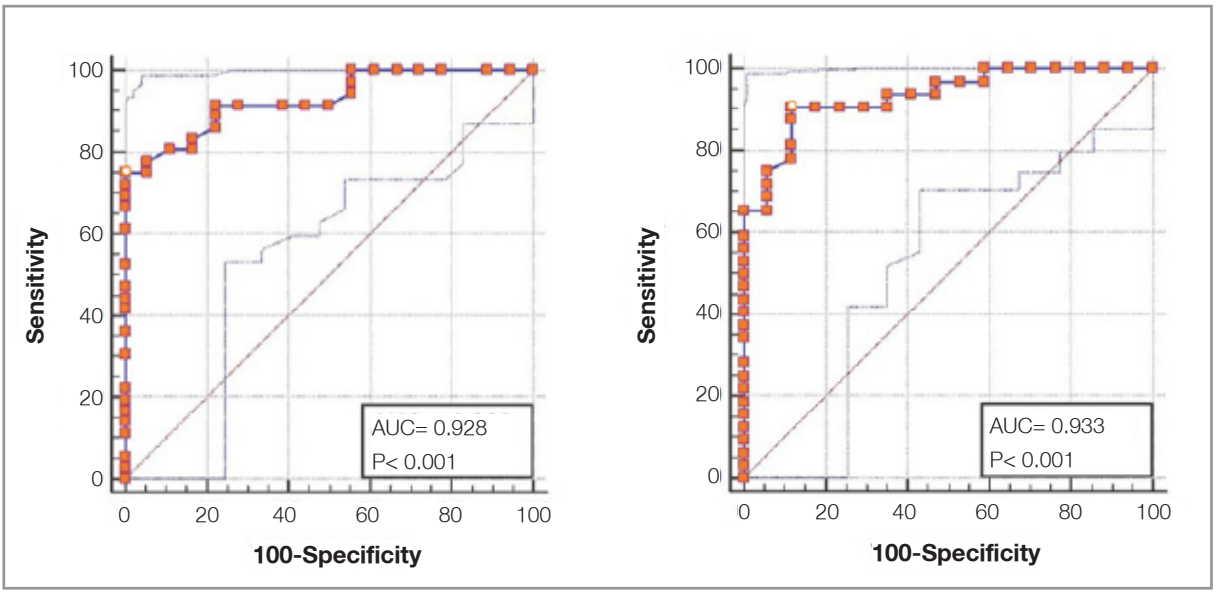

Figure 2a and 2b. ROC analysis of benign-metastatic lymph nodes ADC and relative ADC values

12 patients received neoadjuvant therapy. According to the Mandard regression analysis, 4 of them responded well to treatment (grades 1 and 2) and 8 of them responded partially to treatment. (grade 3, 4). Compared with the partial response, in the group with a good answer, there was a statistically significant increase in ΔADC values (p= 0.004) (Table 2d).

There was a weak and negative correlation between histopathologic tumor volume and ADC values, but this correlation was statistically insignificant (r= - 0.076; p= 0.66).

DISCUSSION

Colorectal cancers are one of the most common cancers worldwide.[13] It is one of the major causes of cancer-related deaths and the rectal cancer mortality rate is 4-10 / 10000 every year.[14] Rectal cancer prognosis depends on the age of the patient, depth of invasion, lymph node metastasis, circumferential resection margin and extramural vascular invasion.[15] The 5-year rectal cancer survey rate was found 66.6%, 88.2% in localized cancer, 70% in regional metastasis, and 14% in distant metastasis.[16]

Rectal cancer treatment depends on the tumor stage. Whether or not to take neoadjuvant therapy depends on tumor depth infiltration and lymph node metastasis. Therefore, preoperative evaluation of rectal cancer is very important in the selection of treatment and estimating the prognosis. There are two main forms of treatment for rectum cancers. While total mesorectal excision is sufficient in the early stages (T1-T2), neoadjuvant chemoradiotherapy is required in locally advanced stages (T3cd, T4, or nodal metastasis). The most important imaging method for staging is MRI. MRI evaluates the rectum wall anatomical layers, perirectal area, mesorectal fascia, and lymph nodes very well. The most accurate evaluation of MRF invasion and circumferential resection margins is done with phase array MRI.[17] In addition, MRI is the best method to demonstrate the spread of rectum cancer to the pelvic organs (prostate gland, uterus, vagina, and perianal muscles).

In the literature, with 1.5 T MRI, T staging accuracy rates range from 67-88%.[18,19,20] Staging accuracy rate of our study was 72.2% and was compatible with the literature. Nine of the 12 T2 stage patients (75%) were staged correctly by MRI. The remaining 3 patients (25%) were staged as T3. High staging in T2 stage cancers is one of the defects of MRI. Inflammatory-desmoplastic changes surrounding the tumor, fibrous tissue and hypervascularity are

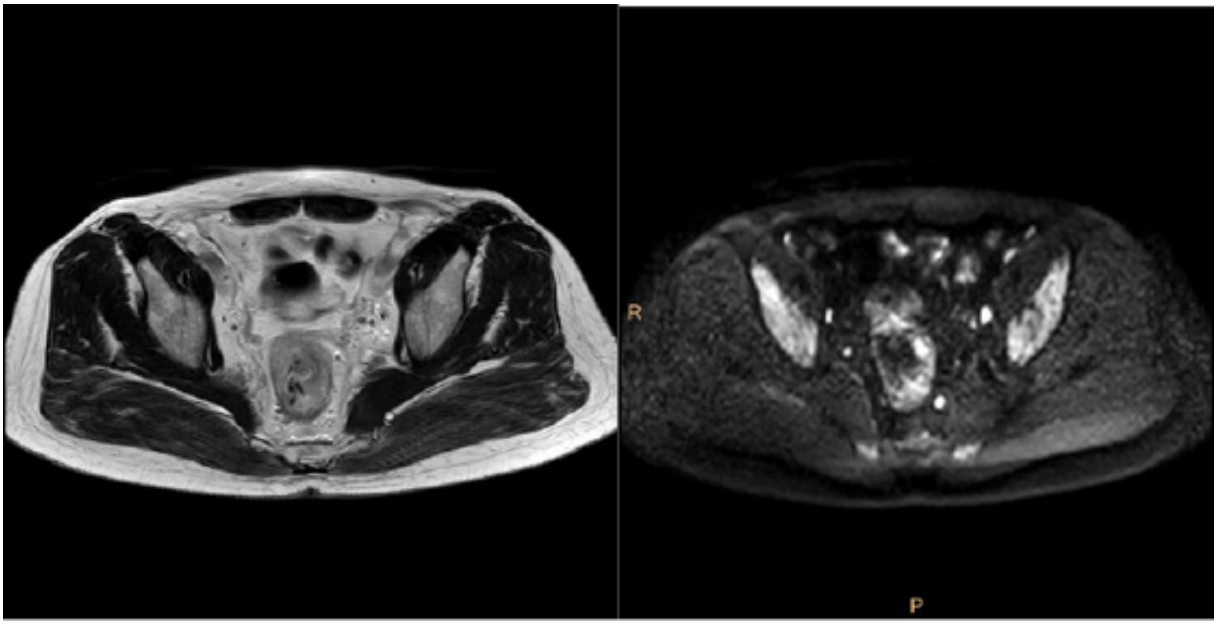

Figure 3. 63 years old, male patient. Histopathology result: pT3N0. According to MRG, perirectal adipose tissue extension of the tumor and DWI hyperintense lymph node (mT3 N1).

factors that cause high staging on MRI. These factors affect the muscularis propria layer and make it difficult to differentiate tumor borders. Tumor localization is another factor for mis-staging.[17,19,21] Nine of 12 T3 stage patients (75%) were correctly staged with MRI. The remaining 3 patients (25%) were staged as T2. The separation of T2 and T3 stage rectal cancers is made according to the perirectal adipose tissue extension. However, it is difficult to distinguish between the T2 stage and early stage T3 tumors and this is an important diagnostic problem of MRI.[21] Tumors with microscopic invasion into the perirectal adipose tissue are less staged with MRI.[19] In our study, early-stage T3 patients were staged as T2 with MRI. But T3 stage tumor ADC values were found significantly lower than T2. Therefore, it was thought that adding DWI and ADC to conventional MRI will increase the T staging accuracy rate and contribute to T2-T3 separation. In addition, the prognosis of extramurally located tumors (T3-T4) is worse than murally located tumors (T1-T2). In our study, ADC values of extramurally located tumors (T3-T4) were significantly lower than murally located T2 tumors. This finding shows that ADC will help about the mural and extramural location of the tumor.

N staging accuracy rate of MRI in the literature ranges between 43-85%.[23,24] The accuracy rate we found with T2 and DWI sequences was consistent with the literature. Diffusion creates image contrast with cellular density differences between tissues.[25] Lymphoid tissue having high cellular density causes restriction in diffusion and hyperintense appears on DWI. This facilitates the detection of lymph nodes. Diffusion has been shown to be a valuable technique in showing lymph nodes.[26] In one study, the total number of lymph nodes detected on DWI was found to be 6% higher than the number of lymph nodes detected by the T2 sequence.[27] In the same study, no significant difference was observed between benign and metastatic lymph nodes in the visual evaluation of lymph nodes by diffusion.[27] According to our findings, diffusion makes mistakes by performing top staging in N staging. This is due to the fact that benign lymph nodes appear hyperintense on DWI. ADC value can be helpful to reduce this error (Figure 3, 4).

Tumor-invasive lymph nodes have a histopathological organization of the primary tumor. Therefore, metastatic lymph nodes are expected to show similar diffusion with the tumor. For this reason, studies were performed with lymph node ADC and

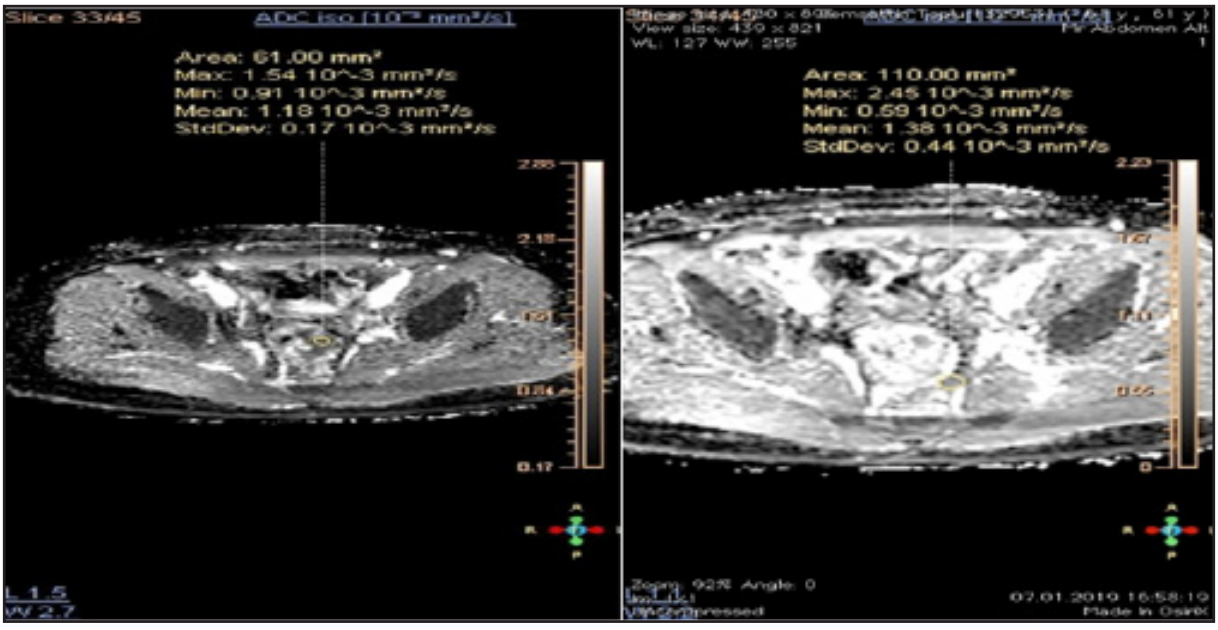

Figure 4. The tumor wall ADC value of the same patient was 0.91 x 10^{-3} mm^2 / sn and was compatible with the extramural ADC value. The ADC value of the DWI hyperintense lymph node was above the lymph node cut-off value with 1.38 x 10^{-3} mm^2 / sn. According to DWI, the patient was N1. But according to ADC cut-off value, it was N0 compatible with histopathology.

relative ADC values. In a study with 1.5T MRI, it was found that ADC and relative ADC values of metastatic lymph nodes decreased significantly compared to benign lymph nodes. According to the relative lymph node ADC cut-off value, the lymph node staging the accuracy rate was 78.5. According to the lymph node ADC cut-off value, the accuracy rate was 74.8. In the same study, according to the size criteria, the lymph node staging accuracy rate was found 62%.[28] Highest accuracy rate was obtained with relative ADC values[28] In our study, according to ADC cut-off values, the accuracy rate of lymph node staging was 83%. This value was higher than the accuracy rate of lymph node staging with T2 and DWI sequence.

Although there are 62 metastatic lymph nodes histopathologically, ADC measurements were made from 33 lymph nodes most likely to be malignant, 5 mm and above. This shows that under 5 mm, micrometastases are also accompanied. In addition, 18 lymph nodes that 5 mm and above were detected in 18 N0 patients. These findings show that the size criterion alone will not be reliable in N staging.[29]

According to the findings of our study, patients receiving neoadjuvant treatment had lower T and N staging accuracy rates with MRI. Edema, inflammation, and necrosis caused by chemoradiotherapy may cause errors in staging with MRI.[20]

According to the histopathology results, no significant difference was found between the primary tumor ADC values of 18 cases with lymph node metastasis and the tumor ADC values of 18 cases with N0. In another study, it was seen that there was no significant correlation between tumor ADC value and N stage and it was compatible with our finding.[30]

Studies have shown that the pathological complete response correlates with increased ADC after chemoradiotherapy.[22] In our study, primary tumor ADC values increased after neoadjuvant therapy and tumor size decreased in all patients. In tumors that respond well to neoadjuvant therapy, the ADC value increase was found significantly higher than the partially responding group. This finding showed that ADC can help predict neoadjuvant therapy efficacy Figure 5).

In our study, ADC values of poorly differentiated tumors were found to be significantly decreased compared with moderately and well-differentiated tumors. In another study, it was similarly shown that there is a significant correlation between ADC

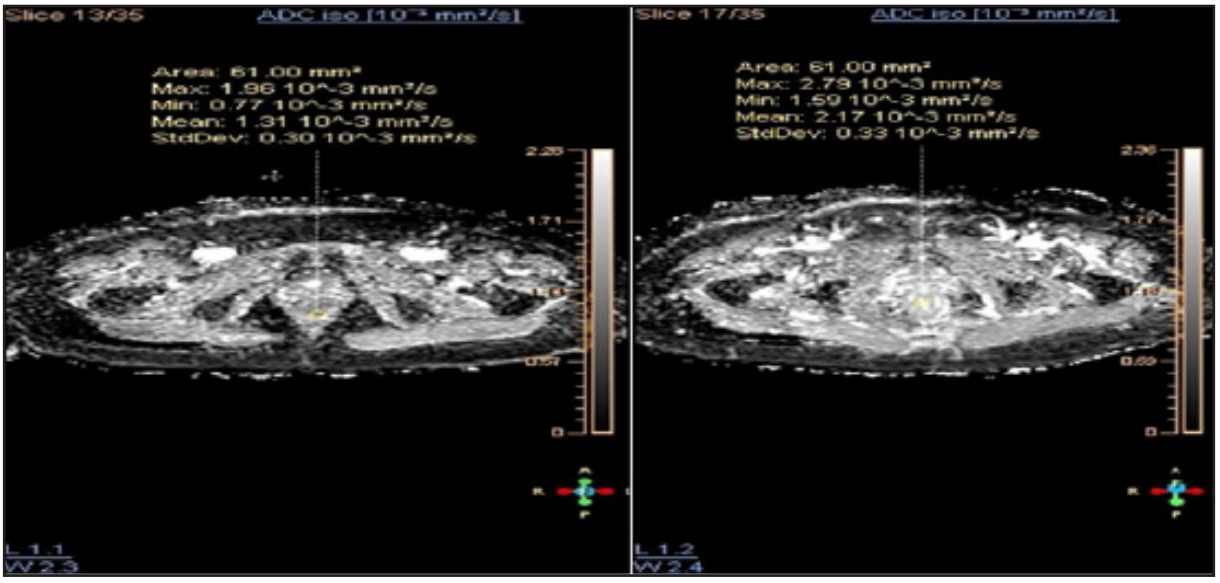

Figure 5. 68 years old, T2N1, patient with a good response to neoadjuvant therapy (Mandard TRG 2). Pretreatment ADC value was 1.31 x 10^{-3} mm^2/sn, post treatment ADC value was 2.17 x 10^{-3} mm^2 / sn. ΔADC was 0.8x10^{-3} mm^2/sn in accordance with good response. Pretreatment ADC value was appropriate with intramural location (T2).

value and tumor differentiation and ADC is a non-invasive potential marker showing tumor aggressiveness.[9]

Considering all findings, primary tumor ADC value helps to predict tumor mural-extramural location, differentiation grade, and response to neoadjuvant therapy. In addition, lymph node ADC values increase the accuracy rate in N staging. As a result, rectum tumor staging should be done according to conventional MRI and DWI sequences. ADC maps of patients should be obtained.

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