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Relationship Between Neoadjuvant Chemoradiotherapy Response and Mesorectum Volume in Rectum Cancer

Ramazan Saygın Kerimoğlu[1], Ebru Esen[2], Mustafa Saraçoğlu[1], İbrahim Babalıoğlu[3], Bekir Turgut[4], İlknur Küçükosmanoğlu[5], Osman Doğru[6]

[1]*University of Health Sciences Turkey, Konya City Hospital, Clinic of Gastrointestinal Surgery, Konya, Turkey*
[2]*University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Surgical Oncology, Ankara, Turkey*
[3]*University of Health Sciences Turkey, Konya City Hospital, Clinic of Radiation Oncology, Konya, Turkey*
[4]*Necmettin Erbakan University, Meram Faculty of Medicine, Department of Radiology, Konya, Turkey*
[5]*University of Health Sciences Turkey, Konya City Hospital, Clinic of Pathology, Konya, Turkey*
[6]*University of Health Sciences Turkey, Konya City Hospital, Clinic of General Surgery, Konya, Turkey*

ABSTRACT

Aim: To investigate the relationship between changes in mesorectum volume (MRV) following neoadjuvant chemoradiotherapy (nCRT) and pathological and clinical response in patients with locally advanced rectum cancer (LARC).

Methods: The study included 39 patients who received nCRT for LARC and underwent surgery between January 2016 and April 2019. The MRV was measured on magnetic resonance imaging (MRI) before and after nCRT. Patients were separated into two groups based on an increase or decrease in MRV following nCRT. The relationships were examined between the 2 groups and the pathological T and N statuses, pre- and post-nCRT T and N statuses, and the degree of MRI regression and pathological regression.

Results: A retrospective analysis was performed on 39 patients, consisting of 19 males and 20 females, with a mean age of 59.3 years (range, 27-80 years). The mean MRV was 116.8 mm^3 (range, 49.9-253.9) before and 115.5 mm^3 (50.9-196.7) after nCRT. There was an increase in MRV in 21 patients and a decrease in 18 patients. In the MRI evaluation, there was no response to nCRT in 4 patients, and in the pathological evaluation, a response could not be determined in 9 patients.

Conclusion: Because this study is one of the first in the literature to investigate the relationship between changes in MRV and response to nCRT, further studies are needed to reach more meaningful results.

Keywords: Rectum cancer, neoadjuvant treatment, mesorectum volume

Introduction

The World Health Organization statistics revealed colorectal cancer to be the second most common malignancy in women (after breast cancer) and the third most common malignancy in men, with a total annual death toll of 861,700 worldwide [1]. One-third of colorectal cancers are rectal cancers. Mesorectal excision after neoadjuvant chemoradiotherapy (nCRT) is the standard treatment for mid- and lower locally advanced rectum cancer (LARC) (T3-4 and/or N+) [2].

The main benefit of nCRT for LARC is to downsize and downstage the tumor to increase the chance of complete resection and obtain better local control [3]. However, several clinical studies have shown extreme variability in the response of LARC to nCRT [4,5]. Although a full pathological and clinical response is achieved with nCRT in approximately 20-30% of patients with rectum cancer, a significant proportion of patients do not respond to nCRT [6-8]. There are many regression grading systems to evaluate the pathological response to nCRT, such as the American Joint Committee on Cancer TRG, Mandard, Dworak, and Ryan Tumor Regression Grading system [9,10]. The Modified Ryan Scheme for Tumor Regression Score is recommended for routine use by the College of American Pathologists [11].

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Address for Correspondence: Ebru Esen MD, University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Surgical Oncology, Ankara, Turkey
Phone: +90 505 831 12 46 **E-mail:** drebruesen@gmail.com **ORCID ID:** orcid.org/0000-0003-3019-0872

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Another advantage of nCRT is that when a clinical full response occurs, the "watch-and-wait" treatment protocol can be applied as a nonsurgical option [12]. Therefore, recent studies have aimed to radiologically estimate pathological responses [13-16]. Of all the suitable imaging methods, magnetic resonance imaging (MRI) is considered the most appropriate because of its broad routine clinical application in the evaluation of rectum cancer, high soft-tissue resolution, and lack of radiation exposure. Some traditional and functional MRI methods have been reported to show advantages in the prediction of tumor response to nCRT [17-19]. Although it has been reported that T and N status affect the response to nCRT, [20-22] there are few studies have investigated other factors that might have an effect. Therefore, the identification of markers that predict response to nCRT is an important issue in the management of LARC.

Since the variables that determine the response of LARC to neoadjuvant therapy are still unknown, variables that affect the response to therapy are still being investigated. The aim of this study was to investigate the relationship between changes in the mesorectum volume (MRV) measured by MRI before and after nCRT and pathological and radiological response in patients with LARC.

Methods

A retrospective screening was performed for patients who received nCRT and underwent surgery at the Konya Training and Research Hospital due to LARC between January 2016 and April 2019. The study included 39 patients (20 females and 19 males, with a mean age of 59.3 years (range, 27-80 years). The inclusion criteria were sufficient quality of MRIs to evaluate MRV and the T and N statuses before and after nCRT, surgery in the Konya Training and Research hospital after nCRT, and were not determined with distant organ metastasis on thoracoabdominal computed tomography (CT).

The first MRI was performed at the time of diagnosis (pre nCRT) and the second MRI (post nCRT) within 1 week before surgery. Grading of the patients was made using the T and N evaluation criteria on MRI. T3 was evaluated as tumor invasion through the muscularis propria into the subserosa or into non-peritonealized perirectal tissues without reaching the mesorectal fascia or adjacent organs, and T4 was evaluated as tumor invasion directly into other organs or structures and/or perforating the visceral peritoneum. Lymph nodes with unfavorable morphology and diameter >5 mm were evaluated as lymph node involvement. N0 was evaluated as no lymph nodes, N1 as 1-3 suspicious nodes, and N2 as ≥4 suspicious nodes. Thoracoabdominal CT examinations were performed in all patients to evaluate distant organ metastasis.

All patients received the same nCRT protocol. For nCRT 6 cycles of FOLFOX therapy are administered. The external beam radiotherapy dose was 50 Gy delivered in 25 daily fractions of 2 Gy five days a week. Concomitant chemotherapy consisted of oral 5-fluorouracil-derivative capecitabine, 825 mg/m^2 b.i.d. Changes in MRV were evaluated using MRI. Patients were separated into 2 groups according to an increase or decrease in MRV. The statistical relationships were investigated by comparing the changes in MRV with the degree of MRI tumor regression and pathological regression.

MRI Evaluation

The MRIs of the patients before and after nCRT were evaluated by an experienced radiology specialist who was blinded to the clinical information of the patients.

All MRIs were acquired on a 1.5T unit (Magnetom aera, Siemens Healthcare, Germany). MRI scans were performed following a standard protocol with a 16-channel phase array pelvic-receiver coil. The MRI tumor regression grade (MrTRG) was used to evaluate regression on MRI (Table 1). TRGs were evaluated on coronal, axial, and sagittal T2W1 MRIs.

Pathology Evaluation

Tissue samples were processed and embedded in paraffin blocks. Slices 5 m thick were cut from the blocks and stained with hematoxylin and eosin. Using the modified Ryan scheme for histopathological examination, the regression scores were evaluated by an independent, experienced pathology specialist (Table 2).

Mesorectum Volume Evaluation

The MRIs were evaluated by an experienced radiation oncologist using the Eclipse Treatment Planning System version 9.8. The mesorectum contours from the piriformis muscle to the level of peritoneal reflection were drawn manually on axial slices to measure the MRV. The net MRV was calculated by subtracting the rectum volume defined in the same way from the defined volume, and the value was recorded as mm^3.

Statistical Analysis

Data obtained in the study were statistically analyzed using Statistical Package for the Social Sciences version 23.0 software (IBM, Armonk, NY, USA). Continuous measurements were presented as mean±standard deviation, median, minimum, and maximum values, and categorical variables were presented as number (n) and percentage (%). For comparisons

Table 1. Magnetic resonance imaging tumor regression classification

Grade	Definition	Response status
1	No tumor signal, only linear scar	Full response
2	A small amount of residual tumor, but predominant fibrotic low signal intensity	Good response
3	Low signal fibrosis and mixed signal density areas moderate but without tumor predominance	Moderate response
4	Mainly signal intensity and minimal fibrotic low signal intensity	Mild response
5	Fibrosis is not evident; only a tumor signal is present	No response

of categorical variables, the chi-squared test or the Fisher's test was used. Agreement between the pre- and post-nCRT MRI results and the pathological results was evaluated using the intraclass correlation coefficient (ICC), interpreted as r ≥0.91: high correlation, 0.90-0.71: good correlation, 0.70-0.51: moderate correlation, 0.50-0.31: low correlation, and ≤0.30: no correlation. The level of statistical significance was accepted as 0.05 for all tests.

Results

The retrospective analysis included 39 patients (20 females and 19 males, with a mean age of 59.3 years (range, 27-80 years). Rectal cancer was present in the distal section in 19 (48.7%) of the patients, in the mid-section in 14 (35.9%), and in the proximal section in 6 (15.4%). The time from nCRT to surgery was ≤12 weeks in 76.9% (30) of the patients and >12 weeks in 23.1% (9). Mesorectal excision was performed in 29 patients, abdominoperineal resection in 9 patients, and abdominoperineal resection together with vaginectomy in 1. The mean MRV was measured as 116.8 mm^3 before nCRT and as 115.5 mm^3 after nCRT. MRV was found to decrease in 18 patients and increase in 21 (Table 3).

When the pathological regression scores were examined, full response was determined to be full response in 4 patients, and no pathological response in 9. Examination of the MrTRG values revealed almost complete response in 5 patients and no response in 4. Pathological regression evaluations according to the modified Ryan scheme and the MrTRG classifications are shown in detail in (Table 4).

The relationships between radiological T and N status and postoperative T and N status were examined using the ICC values. Agreement with the MRI evaluations was low before nCRT (0.19 and 0.42; 0.50-0.31) and moderate after nCRT (0.63 and 0.64; 0.70-0.51) (Table 5).

Table 2. Modified Ryan scheme

Grade	Definition	Response status
0	No viable cancer cells	Full response
1	Single cells or occasional small groups of	Almost full response
2	Residual cancer with evident tumor regression, but greater than single cells or occasional small groups of cancer cells	Partial response
3	Extensive residual cancer with no evident tumor regression	Poor response or no response

Table 3. Demographic and clinical characteristics of patients

	Mean±SD	Median (minimum-maximum)
Age (years)	59.3±11.6	59 (27-80)
	n (%)	
Gender		
Female	20 (51.3)	
Male	19 (48.7)	
Location		
Distal	19 (48.7)	
Middle	14 (35.9)	
Proximal	6 (15.4)	
Surgical interval (weeks)		
<12	30 (76.9)	
>12	9 (23.1)	
Surgery performed		
TME	29 (74.4)	
APR	9 (23.1)	
APR+vaginectomy	1 (2.6)	
MRV		
Decreased	18 (46.2)	
Increased	21 (53.8)	
	Mean±SD	**Median (minimum-maximum)**
Pre-nCRT MRV (mm^3)	116.8±43.7	110.8 (49.9-253.9)
Post-nCRT MRV (mm^3)	115.5±36.9	108.4 (50.9-196.7)
MRV difference	-1.36±28.6	2.7 (-72-62.4)

SD: Standard deviation, MRV: Mesorectum volume, nCRT: Neoadjuvant chemoradiotherapy

The relationships were examined of the increase or decrease in MRV after nCRT with gender, tumor localization, time to surgery, pathological T and N statuses, pre- and post-nCRT MRI T and N statuses, modified Ryan scores and MrTRG were examined. No statistically significant correlation was observed between the variables examined and the changes in MRV ($p>0.05$). The findings are shown in detail in (Table 6).

The relationship between pre- and post-nCRT MRV values and the pathological and radiological response was evaluated by re-classifying patients with grades 0, 1, and 2 in the modified Ryan scheme as pathological response present, and no response in those with grade 3, and radiological response present in patients with grades 1, 2, 3, and 4, and no response in those with grade 5. No statistically significant differences were found between pre- and post-nCRT MRV and pathological response. The relationship between pre- and post-nCRT MRV values and radiological response was found to be more significant than the pathological response, but at $p=0.2$, the difference was not statistically significant in either group (Table 7).

Table 4. Distribution of MrTRG and modified Ryan scores of patients

	n (%)
Modified Ryan score	
0	4 (10.3)
1	8 (20.5)
2	18 (46.2)
3	9 (23.1)
MrTRG	
1	5 (12.8)
2	7 (17.9)
3	13 (33.3)
4	10 (25.6)
5	4 (10.3)

MrTRG: Magnetic resonance imaging tumor regression grade

Discussion

Predicting the pathological response to nCRT in the preoperative period is important for determining which patients can be followed up without surgery under a "watch-and-wait" protocol. In surgeries performed after nCRT, a temporary or permanent ostomy is opened in most patients, which has negative effects on quality of life. Various clinical parameters were used to estimate the pathological response to nCRT. There are studies in the literature that have examined the relationship of response to nCRT with clinical parameters, such as tumor size, distance to the anal verge, and T and N status [20-25]. Although various studies have found a relationship between tumor size and response to nCRT, different methods were used in those studies to evaluate tumor size such as endorectal ultrasound, digital rectal examination and flexible endoscopy [20-24]. The relationship between distance to the anal verge and response to nCRT has not been fully clarified, and its value as a predictive marker is unclear [25,26]. Although a full clinical and pathological response after nCRT has been observed more frequently in T1-2 tumors, this rate has been shown to be lower in lymph node positivity [20-22]. Moreover, only examining T and N status is insufficient for individual patient response evaluation.

There are studies in the literature that have aimed to predict which patients will respond to nCRT with imaging methods in LARC. MRI radionic features of mesorectal fat can be used to predict pathological complete response, local and distant recurrences, and T and N categories after treatment [14,15]. To the best of our knowledge, this study is one of the first to investigate the role of MRV changes in the estimation of pathological response to nCRT in the treatment of LARC.

In a previous study that evaluated the relationship between mesorectal fatty tissue volume and response to nCRT, it was shown that when MRV exceeded 69.4 mL, the rates of pathological response increased [13]. In that study, the median MRV value was found to be 85.7 mm^3 (21.2-269.0), whereas in the current study, the MRV values measured with

Table 5. Compatibility of pathology data with MRI evaluations before and after nCRT

	Pathology	Pre-nCRT MRI	Post-nCRT MRI	Interclass correlation (95% CI)	
	n (%)	n (%)	n (%)	Pat&PreMR	Pat&PostMR
T					
T0	7 (17.9)	-	4 (10.3)	0.19 (-0.51-0.58)	0.63 (0.29-0.80)
T1	4 (10.3)	-	7 (17.9)		
T2	9 (23.1)	11 (28.2)	16 (41.0)		
T3	16 (41.0)	25 (64.1)	11 (28.2)		
T4	3 (7.7)	3 (7.7)	1 (2.6)		
N					
N0	28 (71.8)	9 (23.1)	26 (66.7)	0.42 (-0.10-0.70)	0.64 (0.30-0.81)
N1	6 (15.4)	22 (56.4)	9 (23.1)		
N2	4 (10.3)	8 (20.5)	4 (10.3)		
N3	1 (2.6)	-	-		

MRI: Magnetic resonance imaging, CI: Confidence interval, nCRT: Neoadjuvant chemoradiotherapy

Table 6. Relationships between variables and increase/decrease in mesorectum volume

	MRV decreased	MRV increased	p
	n (%)	n (%)	
Gender			
Female	10 (55.6)	10 (47.6)	0.751
Male	8 (44.4)	11 (52.4)	
Tumor localization			
Distal	11 (61.1)	8 (38.1)	0.356
Mid	5 (27.8)	9 (42.9)	
Proximal	2 (11.1)	4 (19.0)	
Surgical interval (weeks)			
<12	12 (66.7)	18 (85.7)	0.255
>12	6 (33.3)	3 (14.3)	
ypT			
ypT0	4 (22.2)	3 (14.3)	0.962
ypT1	2 (11.1)	2 (9.5)	
ypT2	4 (22.2)	5 (23.8)	
ypT3	7 (38.9)	9 (42.9)	
ypT4	1 (5.6)	2 (9.5)	
ypN			
ypN0	15 (83.3)	13 (61.9)	0.132
ypN1	2 (11.1)	4 (19.0)	
ypN2	0 (0.0)	4 (19.0)	
ypN3	1 (5.6)	0 (0.0)	
Modified Ryan score			
0	3 (16.7)	1 (4.8)	0.619
1	4 (22.2)	4 (19.0)	
2	7 (38.9)	11 (52.4)	
3	4 (22.2)	5 (23.8)	
MrTRG			
1	2 (11.1)	3 (14.3)	0.601
2	5 (27.8)	2 (9.5)	
3	6 (33.3)	7 (33.3)	
4	4 (22.2)	6 (28.6)	
5	1 (5.6)	3 (14.3)	
MRI T before nCRT			
T2	4 (22.2)	7 (33.3)	0.617
T3	13 (72.2)	12 (57.1)	
T4	1 (5.6)	2 (9.5)	
MRI N before nCRT			
N0	5 (27.8)	4 (19.0)	0.388
N1	11 (61.1)	11 (52.4)	
N2	2 (11.1)	6 (28.6)	
MRI T after nCRT			
T0	2 (11.1)	2 (9.5)	0.352
T1	5 (27.8)	2 (9.5)	
T2	5 (27.8)	11 (52.4)	
T3	6 (33.3)	5 (23.8)	
T4	0 (0.0)	1 (4.8)	
MRI N after nCRT			
N0	11 (61.1)	15 (71.4)	0.301
N1	6 (33.3)	3 (14.3)	
N2	1 (5.6)	3 (14.3)	

MrTRG: Magnetic resonance imaging tumor regression grade, MRV: Mesorectum volume, nCRT: Neoadjuvant chemoradiotherapy

MRI were 110.8 mm^3 before nCRT and 108.4 mm^3 after nCRT. The difference between the values in these two studies was attributed to the measurement with MRI in the current study and with CT in the previous study, and no clear criteria have been determined for MRV measurement.

Some studies have shown that surgical outcomes after colon cancer surgery are related to the visceral fatty area rather than BMI [27-30]. In a study that investigated the clinical importance of mesorectal fatty tissue, it was shown that as the mesorectal fatty area (cm^2) increased, survival increased [31]. Survival analysis was not performed in the current study, and as the mesorectal surface area was not considered to be more important, the MRV measurement was performed as a 3-dimensional measurement.

As the number of patients in this study was low in each of the MrTRG grade and modified Ryan grade groups, the patients were classified as those with and without a pathological response, and the relationship between the MRI findings and the increase or decrease in MRV was evaluated. However, there was still not found to be any statistically significant relationship between the groups.

A moderate-level correlation was determined between the pathological ypT and ypN values and the T and N statuses evaluated by MRI after nCRT. It can be considered that future studies with larger patient populations will be able to reach higher correlation values, and thus, statistically significant results will emerge.

Although no statistically significant difference was found in this study, it is important to examine the relationship between changes in MRV and both postoperative T and N status, as well as the clinical regression grade values (MrTRG and Ryan regression grade).

Table 7. Relationship of MRV with pathological and radiological response

	Pathological response (+) Mean±SD	Pathological response (-) Mean±SD	p	MRI response (+) Mean±SD	MRI response (-) Mean±SD	p
Pre-nCRT MRV (mm^3)	118.3±43.8	111.9±45.3	0.7	119.9±44.9	89.3±103	0.2
Post-nCRT MRV (mm^3)	117.6±39.6	108.3±26.9	0.5	117.8±38.1	94.6±13.5	0.2

MrTRG: Magnetic resonance imaging (MRI) tumor regression grade, MRV: Mesorectum volume, nCRT: Neoadjuvant chemoradiotherapy SD: Standard deviation

Study Limitations

The limitations of this study could be said to be that there was no analysis of total body fat volume, subcutaneous fat volume, visceral fat volume, and BMI values, the patient population was small, there is no standardization in MRV measurements, and it will be better to have two reviewers who can independently evaluate the MRIs and pathologies.

Conclusion

In conclusion, although no significant relationship was determined between the increase or decrease in MRV and the response to nCRT, this is the first study to investigate this subject. There is a need for further studies with larger patient groups and using different imaging techniques, which will help overcome the limitations of this study and better reflect the importance of changes in MRV.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Konya Training and Research Hospital (decision no: 27-08, date: 04.07.2019) and conformed to the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: R.S.K., E.E., O.D., Design: R.S.K., E.E., O.D., Data Collection or Processing: R.S.K., E.E., M.S., Analysis or Interpretation: İ.K., Literature Search: R.S.K., E.E., M.S., İ.B., B.T., Writing: R.S.K., E.E.

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