Original Article

The Relationship Between the Response to Neoadjuvant Chemoradiotherapy and Mesorectum Volume in Rectum Cancer

Rektum Kanserinde Neoadjuvan Kemoradyoterapi Yanıtı ile Mezorektum Hacmi Arasındaki İlişki

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ABSTRACT

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

Methods: The study included 39 patients who received nCRT because of LARC and underwent surgery between January 2016 and April 2019. The MRV values were measured on magnetic resonance imaging (MRI) before and after nCRT. The patients were separated into two groups as those with 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: Retrospective analysis was made of 39 patients comprising 19 males and 20 females with a mean age of 59.3 years (range, 27-80 years). The mean MRV value was 116.8 mm^3 (range, 49.9-253.9) before nCRT and 115.5 mm^3 (50.9-196.7) after nCRT. There was determined to be an increase in MRV in 21 patients, and a decrease in 18 patients. In the MRI evaluation there was no response to nCRT in four patients, and in the pathological evaluation, a response could not be determined in nine patients.

Discussion and Conclusion: Since this study is one of the first studies 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 volüme

ÖZET

Giriş ve Amaç: Lokal ileri rektum kanserli (LARK) hastalarda neoadjuvan kemoradyoterapi (nKRT) ile ilişkili mezorektum hacmindeki (MRV) değişikliklerin patolojik ve klinik yanıtla ilişkisini araştırmak.

Yöntem ve Gereçler: Çalışmaya Ocak 2016-Nisan 2019 tarihleri arasında LARK nedeniyle nKRT alan ve ameliyat edilen 39 hasta dahil edildi. MRV değerleri nKRT öncesi ve sonrası manyetik rezonans görüntüleme (MRG) ile ölçüldü. Hastalar nKRT sonrası MRV'de artış veya azalma olanlar olarak iki gruba ayrıldı. İki grup ile patolojik T ve N durumları, nKRT öncesi ve sonrası T ve N durumları ve MRG gerilemesi ve patolojik gerileme derecesi arasındaki ilişkiler incelendi.

Bulgular: Yaş ortalaması 59,3 (27-80 yıl) olan 19 erkek, 20 kadın toplam 39 hastanın retrospektif analizi yapıldı. nKRT öncesi ortalama MRV değeri 116,8 mm^3 (aralık, 49,9-253,9), nCRT sonrası 115,5

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mm^3 (50,9-196,7) idi. 21 hastada MRV'de artış, 18 hastada azalma saptandı. MRG değerlendirmesinde dört hastada nCRT'ye yanıt alınamadı, patolojik değerlendirmede dokuz hastada yanıt saptanamadı.
Tartışma ve Sonuç: Bu çalışma literatürde MRV'deki değişiklikler ile nKRT'ye yanıt arasındaki ilişkiyi araştıran ilk çalışmalardan biri olduğundan, daha anlamlı sonuçlara ulaşabilmek için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Rektum kanseri, Neoadjuvan tedavi, Mezorektum hacmi

Introduction

World Health Organization (WHO) statistics reveal that colorectal cancer is 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. Meso-rectal excision after neoadjuvant chemoradio-therapy (nCRT) is accepted as the standard treatment in mid and lower locally advanced rectum cancer (LARC) (T3-4 and/or N+) [2].

The main benefit of nCRT in 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]. While a full pathological and clinical response is obtained with nCRT in approximately 20-30% of patients with rectum cancer, a significant proportion of patients do not respond to nCRT [6, 7, 8]. There are many regression grading systems to evaluate the pathological response to nCRT, such as the American Joint Committee on Cancer (AJCC) TRG system, the Mandard, Dworak Systems and the Ryan Tumour Regression Grading system [9, 10]. The Modified Ryan Scheme for Tumour Regression Score is recommended for routine use by the College of American Pathologists [11].

Another advantage of nCRT is that when there is a clinical full response, the "watch-and-wait" treatment protocol can be applied as a non-surgical option [12]. Therefore, recent studies have aimed to estimate the pathological response radiologically [13, 14, 15, 16]. Of all the suitable imaging methods, magnetic resonance imaging (MRI) is accepted as the most appropriate method because of the broad routine clinical application in the evaluation of rectum cancer, showing high soft tissue resolution and that there is no radiation exposure. Some traditional and functional MRI methods have been reported to show some advantages in the prediction of tumour response to nCRT [17, 18, 19]. Although it has been reported that T and N statuses affect the response to nCRT, [20, 21, 22] there are few studies related to other factors that might have an effect. Therefore, the determination of markers that can predict the response to nCRT is an important issue in the management of LARC.

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

Materials and Methods

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

Table 1. MRI Tumor Regression Classification

Grade	Definition	Response status
1	No tumour signal, only linear scar	Full response
2	A small amount of residual tumour, but predominant fibrotic low signal intensity	Good response
3	Low signal fibrosis and mixed areas with signal density at a moderate level but no tumour predominance	Moderate ressponse
4	Mainly signal intensity and minimal fibrotic low signal intensity	Mild response
5	Fibrosis not evident, only a tumour signal present	No response

Table 2. Modified Ryan Scheme

Grade	Definition	Response Status
0	no viable cancer cells	Full response
1	single cells or occasional small groups of cancer cells	Almost full response
2	residual cancer with evident tumor regression but morethan single cells or occasional small groups of cancer cells	Partial response
3	extensive residual cancer with no evident tumorregression	Poor response or no response

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-peritonealised perirectal tissues without reaching the mesorectal fascia or adjacent organs, T4 was evaluated as tumor invasion directly into other organs or structures and/or perforating the visceral peritoneum. Lymph nodes with unfavorable morphology and a 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. Thoraco-abdominal CT examinations were made of all patients to evaluate distant organ metastasis.

All patients received same nCRT protocol. For neoadjuvant chemothrapy 6 cycles of FOLFOX therapy 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 derivate Capecitabine, 825 mg/m^2 b.i.d. Changes in MRV were evaluated with MRI. The patients were separated into 2 groups according to an increase or decrease in MRV. Statistical relationships were investigated through comparisons of the changes in MRV with the degree of MRI tumour regression and the degree of 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 the MRIs were acquired on a 1.5T unit (Magnetom aera, Siemens Healthcare, Germany). The MRI scans were taken following a standard protocol with a 16-channel phase array pelvic-receiver coil. The MRI tumour regression grade (MrTRG) classification was used to evaluate regression on MRIs (Table 1). The tumour regression grade was evaluated on coronal, axial, and sagittal T2W1 MRIs.

Pathology Evaluation

Tissue samples were processed then embedded in paraffin blocks. Slices 5 micron in thickness were cut from the blocks and stained with hematoxylin and eosin. Using the modified Ryan scheme in the histo-pathological examination, the regression scores were evaluated by an independent, experienced pathology specialist (Table 2).

Table 3. Demographic and Clinical Characteristics of the Patients

	Mean±SD	Median (Min-Max)
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 perfomed		
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 (Min-Max)
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)

Mesorectum Volume Evaluation

The MR images 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 the 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 this defined volume and the value was recorded as mm3.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn. 23.0 software (IBM, Armonk, NY, USA). Continuous measurements were stated as mean ± standard deviation (SD), or median, minimum and maximum values, and categorical variables as number (n) and percentage (%). In the comparisons of categorical variables, the Chi-square test or the Fisher test was used. Agreement of the pre and post-nCRT MRI results with the pathological results was evaluated with 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 in all the tests was accepted as 0.05.

Results

Retrospective analysis was made of 39 patients, comprising 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 nine, and abdominoperineal resection together with vaginectomy in one. The mean MRV was measured as 116.8mm^3 before nCRT and as 115.5mm^3 after nCRT. The MRV was found to have decreased in 18 patients and increased in 21 (Table 3).

When the pathological regression scores were examined, there was determined to be full response in four patients, and no pathological response in nine. Examination of the MrTRG values showed an almost full response in five patients and no response in four. The pathological regression evaluations according

Table 4. Distribution of the MRI TRG and Modified Ryan Scores of the 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)

to the modified Ryan scheme and the MrTRG classifications are shown in detail in (Table 4).

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

The relationships were examined of the increase or decrease in MRV after nCRT with gender, tumour localisation, time to surgery, pathological T and N statuses, pre and post-nCRT MRI T and N statuses, modified Ryan scores, and MrTRG. No statistically significant correlation was determined 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-classifiying patients with grade 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 MrTRG grade 1, 2, 3, and 4, and no response in those with grade 5. No statistically significant difference was found between the pre and post-nCRT MRV and pathological response. The relationship between the pre and post-nCRT MRV values and the radiological response was found to be more significant compared to the pathological response, but at P=0.2, the difference was not statistically significant in either group (Table 7).

Discussion

Predicting the pathological response to nCRT in the preoperative period is important in respect of determining which patients can be followed up without surgery under a “watch-and-wait” protocol. In operations performed after nCRT, a temporary or permanent ostomy is opened in most patients and this has negative effects on quality of life. Various clinical parameters are used to estimate the pathological response to nCRT. There are studies in literature that have examined the relationship of response to nCRT with clinical parameters such as tumour size, distance to the anal verge, and T and N status [20,21 22, 23, 24, 25]. Although various studies have found a relationship between tumour size and response to nCRT, different methods were used in those studies to evaluate tumour size such as endorectal ultrasound, digital rectal examination, and flexible endoscopy [20, 21, 22, 23, 24]. As the relationship between distance to the anal verge and response to nCRT has not been fully clarified, the value of this as a predictive marker is unclear [25, 26]. Although a full clinical and pathological response after nCRT has been seen more in T1-2 tumours, this rate has been shown to be lower in lymph node positivity [20, 21, 22]. Moreover, only examining T and N statuses is insufficient for an individual patient-based response evaluation.

There are studies in literature that have aimed to predict which patients will respond to nCRT with imaging methods in LARC. MRI radiomic 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 studies in the literature to have investigated the role of MRV changes in the estimation of pathological response to nCRT in the treatment of LARC.

Table 5. Compatibility of Pathology Data with MRI Evaluations Before and After nCRT

	Pathology	Pre- nCRT MRI	Post- nCRT MRI	Inter Class 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)	-	-			

In a previous study that evaluated the relationship of mesorectal fatty tissue volume with response to nCRT, it was shown that when MRV exceeded 69.4ml, the rates of pathological response increased [13]. In that study, the MRV median value was found to be 85.7mm^3 (21.2-269.0), whereas in the current study, the MRV values measured with 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 thought to be due to the measurement with MRI in the current study and with CT in the previous study, and that no clear criteria have been determined for MRV measurement.

Some studies have shown that the surgical results after colon cancer surgery are related to the visceral fatty area rather than BMI [27, 28, 29, 30]. In a study that investigated the clinical importance of mesorectal fatty tissue, it was shown that as the mesorectal fatty area (cm2) increased, there was an increase in survival [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 taken as a 3-dimensional measurement.

As the number of patients in this study was low in each of the MrTRG grade and the modified Ryan grade groups, the patients were classified as those with and without a pathological response, and the relationship between the MRI findings and 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 with 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.

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

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, that the patient population was small, there is no standardisation has been determined in MRV measurements, it will be better to have two reviewers who can independently evaluate the MRIs and pathologies.

Table 6. Relationships between Variables and Increase/Decrease in Mesorectum Volume

		MRV decreased n (%)	MRV increased n (%)	p
Gender				
	Female	10 (55.6)	10 (47.6)	
	Male	8 (44.4)	11 (52.4)	0.751
Tumour Localisation				
	Distal	11 (61.1)	8 (38.1)	
	Mid	5 (27.8)	9 (42.9)	
	Proximal	2 (11.1)	4 (19.0)	0.356
Surgical interval(weeks)				
	<12	12 (66.7)	18 (85.7)	
	>12	6 (33.3)	3 (14.3)	0.255
ypT				
	ypT0	4 (22.2)	3 (14.3)	
	ypT1	2 (11.1)	2 (9.5)	
	ypT2	4 (22.2)	5 (23.8)	
	ypT3	7 (38.9)	9 (42.9)	0.962
	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)	
	2	5 (27.8)	2 (9.5)	
	3	6 (33.3)	7 (33.3)	0.601
	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)	
	T1	5 (27.8)	2 (9.5)	
	T2	5 (27.8)	11 (52.4)	0.352
	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)	
	N1	6 (33.3)	3 (14.3)	0.301
	N2	1 (5.6)	3 (14.3)	

Table 7. The relationship of MRV with Pathological and Radiological Response

	Pathological response (+) Mean±SD	Pathological response (-) Mean±SD	*p*	MR response (+) Mean±SD	MR response (-) Mean±SD	*p*
Pre nCRTMRV (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*

Conclusion

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

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