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Can the mesorectal fat tissue volume be used as a predictive factor in foreseeing the response to neoadjuvant chemoradiotherapy in rectum cancer? A CT-based preliminary study

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Abstract

Purpose This study was to investigate the effect of mesorectal fat tissue volume (MRV) on the pathological response to neoadjuvant chemoradiotherapy (nCRT) in patients with locally advanced rectal cancer.

Methods 88 patients who had been diagnosed with locally advanced rectal cancer between January 2017 and June 2020 were reviewed retrospectively. The total abdominal, subcutaneous, visceral, and mesorectal fatty tissue components were measured semiquantitatively by two radiologists using computed tomography (CT)-based findings. The patients were divided into two groups as those with and without a pathological response to nCRT. The relationship of MRV with the other fat tissue components of the body was also evaluated.

Results We performed a retrospective analysis of 88 patients (mean age 62.7 years [range, 33–90 years]; 31 males and 57 females). A positive response to nCRT was present in 47 patients. There were 59 patients with stage 3 disease. 46 patients demonstrated lymph node involvement. The mean MRV was 69.6 ± 31.0 ml in no-response group and 105.8 ± 47.5 ml in response-positive patients ($p < 0.05$). MRV showed the highest correlation with visceral fat volume (VFV). There was a negative correlation between the MRV and the N stage. A cut-off value of ≥ 69.4 for MRV predicted the repsonse to nCRT, with 82.9% sensitivity and 58.5% specificity [AUC: 0.757 (0.653–0.842), $p < 0.001$] in receiver operating characteristic (ROC) curve analysis

Conclusions MRV can be used as a novel parameter in predicting of pathological response to nCRT in locally advanced rectal cancer patients.

Keywords Rectum cancer · Mesorectal fat tissue volume · Neoadjuvant chemoradiotherapy · Pathological response

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Introduction

Colorectal cancer is a major health issue, with approximately 1,400,000 new cases and 700,000 deaths originating globally every year. In addition to being the third most common malignancy, it is also the fourth most frequent cause of cancer-related deaths [1]. Almost a third of all colorectal cancers are rectal cancers [2]. The frequency of rectal cancer varies from country to country [2]. Although the curative treatment of early-stage rectal cancer is surgery, the prognosis differs in patients with advanced tumor stage and/or positive lymph nodes, which is defined as locally advanced rectal cancer. In these patients, neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision is the standard choice of therapy for the local control and cure of the disease [3, 4]. Tumor downsizing has been reported in patients undergoing nCRT, and a complete pathological response was noted in 15–27% of these patients [5, 6]. Magnetic resonance imaging (MRI), endoscopic ultrasonography, and digital examination are the most suitable methods to evaluate tumor response and morphology following nCRT [7–9]. Assessment of response to neoadjuvant chemoradiotherapy (nCRT) is another crucial issue in rectal cancer. Although the RECIST system provides great help for this purpose, there is still no specific evaluation system that has gained wide acceptance and falls within the guidelines. Numerous systems are available for assessing of the pathological response to nCRT, such as those labeled, The American Joint Committee on Cancer (AJCC), the Mandard and Dworak Systems, and the RyanTumor Regression Grading (TRD) System [10, 11]. Recently, radiomics studies have been performed to radiologically predict pathological response [12–14].

It has been reported that the presence of lymph node involvement and mesorectal tumor invasion affect the response to nCRT [15]. However, the number of detailed studies on other influencing factors is rather limited. The purpose of this study was to evaluate the effect of mesorectal fat tissue volume (MRV) on the pathological response to nCRT in patients with locally advanced rectal cancer or rectal cancer with metastatic lymph nodes. Another objective of the study was to investigate the relationship of MRV with body mass index (BMI) and abdominal fat tissue components.

Materials and methods

This study was approved by the Ethical Committee. It was conducted in full accordance with the guidelines of the Declaration of Helsinki. 170 patients who had been diagnosed with rectal cancer in our hospital between January 1, 2017 and June 30, 2020 were retrospectively analyzed. 88 patients who had undergone a pre-treatment colonoscopic biopsy procedure and received a pathological diagnosis of rectal cancer were included in the study. The staging of the patients was done by the utilization of the T and N evaluation criteria, by means of MRI. Lymph nodes with an unfavorable morphology and a diameter above 5 mm were evaluated as pathologic, in terms of lymph node involvement. N0 was evaluated as no lymph nodes, whereas N1 was evaluated as 1–3 suspicious nodes, and N2 as 4 or more suspicious nodes. Thoracoabdominal computed tomographic (CT) examinations were performed in order to evaluate distant organ metastases.

These patients participating in the present study had middle and inferior rectal involvement and were operated within 4–8 weeks following nCRT. The demographic data of the patients, such as age, gender, height, weight, BMI, and medical history, were obtained from the hospital information service (HIS) database. Those with inadequate CT image quality, as well as with a history of pelvic surgery and/or pelvic CRT or radiotherapy, and a pelvic mass and fluid collection which might impair evaluation, were excluded from the study. The postoperative pathological response was evaluated by a single pathologist, to maintain an evaluation standard. The modified Ryan scoring system was utilized for pathological evaluation [16]. This system renders the pathological response in the following terms: complete response, if no vital cancer cells are present; near-complete response, if a single or few cancer cells are present; minimal response, if there is a mild regression in tumor cells; and finally no response, if there is no regression of the tumor. Because the distribution of our patients was not homogenous, we defined the complete and partial response groups as response-positive, and the minimal-response and no-response groups as response-negative, categories.

Capecitabine (2×825 mg/m^2) was administered to the patients, as the chemotherapeutic agent. The dose required for radiotherapy in rectal cancer to treat microscopic disease with conventional fractionation is 45–50.4 Gy. The radiation dose received by the patient varies depending on the presence of T3 and T4 or lymph nodes. Mesorectal adipose tissue volume does not change the radiotherapy dose. However, irradiation is done in 3-dimensions to cover the entire mesorectum.

Volumetric measurements of abdominal and mesorectal adipoid tissue

Imaging was performed by a 128-detector MDCT system (Philips Ingenuity 128, Eindhoven, The Netherlands). The technical parameters utilized were as follows: 120 kvP,

200–400 mAs automatic tube current modulation, rotation time 0.42 s, pitch 0.6, slice thickness: 1 mm, for all phases. Contrast-enhanced scanning was performed by the injections of saline, non-ionic iodinated contrast media, and finally 20 ml saline, in sequential order, all via the antecubital vein, and by means of an automatic infusion pump. Oral contrast was administered. All measurements were performed at the portal venous phase. During the measurements and evaluations, all CT images were examined at the soft-tissue window. These images were evaluated at a workstation (Intelli SpacePhilips [IPS], The Netherlands); and abdominal and mesorectal adipose tissue volumes were calculated (Fig. 1a). − 130 to − 30 HU values were utilized for adipose tissue voxels. The abdominal adipose tissue compartment is the space between the diaphragmatic esophageal hiatus and the symphysis pubis. This visceral fatty tissue contains the mesenteric, subperitoneal, and retroperitoneal fatty compartments [17]. The subcutaneous fatty tissue is defined as the region localized between the muscle layers of the abdominal wall, together with the paraspinal subcutaneous fatty compartments [17]. In accordance with the protocol of our study, the total adipose tissue volume was calculated first, followed by the measurement of the visceral and subcutaneous fat tissue volumes (Fig. 1b–d). The mesorectal adipose tissue compartment was defined as the space between the rectosigmoid junction proximally, and the most distal axial sections devoid of perirectal fat density, distally. The adipose tissue volume surrounding the rectum was evaluated. Special attention was paid to the interfaces of the mesorectal fascia and other visceral organs. These structures were the intestines, female genitalia, male bladder, seminal vesicles, and the prostate. During the measurement process, all images created by the software were checked by two radiologists, against the possibility of the erring; and corrections were made by these radiologists, if necessary. Manually performed corrections were made by the utilization of the "editing tool", in order to prevent the inclusion of solid organs, intestines, vessels, and fat-free tissues like the skeleton, into the measurement areas. The visceral, subcutaneous, and mesorectal fat tissue volumes were measured in millimeters and automatically, by the software program. All measurements were performed by two radiologists, in consensus. For the measurements, all images obtained from the software were used. No extrapolation procedures such as addition and multiplication were utilized. This made possible the calculation of the real adipose tissue volumes.

Statistics

Statistical methods

For the descriptive statistics of the data, the mean value, standard deviation, median, lowest and highest values, frequency, and ratio values were obtained. The distribution of the variables was measured by the utilization of the Kolmogorov–Smirnov test. The independent variable t test, the Kruskal–Wallis, and the Mann–Whitney U tests were used for the analysis of the quantitative independent data. The Chi-square test was utilized for the analysis of the qualitative

Fig. 1 Axial section tomography images show measurements of **a** total abdominal adipose tissue, **b** visceral adipose tissue, **c** mesorectum adipose tissue, a patient with nCRT response, **d** mesorectum adipose tissue, a patient with nCRT non-response
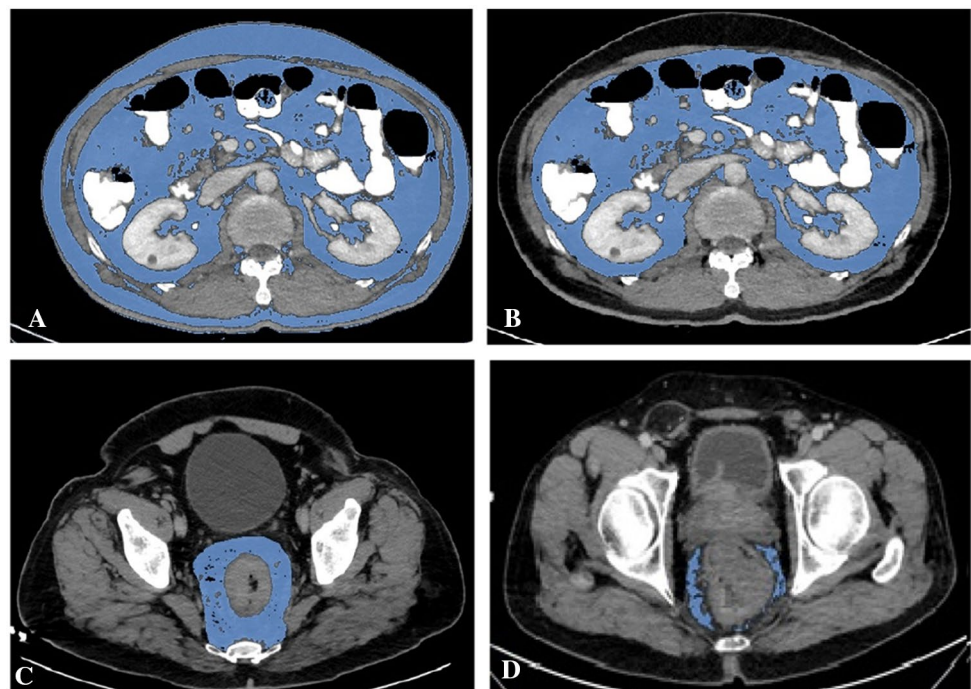
independent data. Correlation analysis was performed by the Spearman correlation analysis method. Receiver operating characteristic curve analysis was used to determine the cut-off value of MRV in predicting the response to nCRT based on the Youden index. The p values under 0.05 were appointed as statistically significant. The SPSS 26.0 statistical software package was utilized for the statistical analyses.

Results

88 patients, 57 of whom were female, were enrolled in the study. The overall mean age of the patients was 62.7 ± 10.8 years (min–max 33–90 years). The mean BMI was 26.6 ± 3.6 kg/m^2 (min–max 19.1–34.9 kg / m^2). 59 patients had stage T3 disease, while 29 had stage T4 disease. 42 patients were defined as N0, while 34 were defined as N1, patients. 12 patients were categorized as N2. The mean total fat volume (TFV) was $11,074 \pm 4208$ ml (min–max 2973–21,988 ml), while the mean visceral fat volume (VFV) was 4213 ± 1777 ml (min–max 1130–9297 ml), and the mean subcutenous far volume (SFV) was 6885 ± 2780 ml (min–max 1843–14,397 ml). The mean MRV was found to be 88.9 ± 44.3 ml (min–max 21.2 ± 269.0 ml). Detailed data are summarized in Table 1.

No statistically significant relationship was found between the mesorectal fat tissue volume (MRV) and patient age. But there was a positive correlation between the MRV and TFV, VFV, body mass index (BMI), weight, and height. The highest correlation was with the VFV, and the r coefficient was calculated as 0.666. Detailed findings are demonstrated at Table 2.

The patients were categorized into certain groups according to their responses to nCRT. These groups were as follows: no response, minimal response, partial or near-complete response, and complete response. As the response rate to nCRT increased, so did the MRV, TFV, VFV, and SFV values (Table 3).

Patients with no or minimal pathological response were evaluated as response-negative cases; while patients with partial or complete response were evaluated as response-positive cases. The mean MRV values were found to be 69.6 ± 31.0 ml for the response-negative groups and 105.8 ± 47.5 ml for the response-positive groups ($p < 0.005$). No statistically significant association was found between the pathological response rates and the BMI, TFV, VFV, and SFV values. The pathological response to nCRT has been found to decrease as the N stage increases ($p < 0.05$). The region of rectal involvement, T stage, age, and gender have been shown to be factors that influence the pathological response rate to nCRT ($p < 0.05$) (Table 4).

A cut-off value of ≥ 69.4 for MRV predicted the response to nCRT, with 82.9% sensitivity and 58.5% specificity

Table 1 The demographic and other detailed findings are demonstrated

	Min–Max	Median	Mean ± SD/n%	
Age (years)	33.0–90.0	64.0	62.7 ± 10.8	
Gender				
Male			31	35.2%
Female			57	64.8%
Height (cm)	152.0–183.0	165.0	164.9 ± 6.6	
Weight (kg)	50.0–104.0	73.5	72.4 ± 11.7	
BMI (kg/m^2)	19.1–34.9	26.4	26.6 ± 3.6	
T				
III			59	67.0%
IV			29	33.0%
N				
0			42	47.7%
I			34	38.6%
II			12	13.6%
Grade				
I			23	26.1%
II			62	70.5%
III			3	3.4%
Location				
Proximal			24	27.3%
Middle			29	33.0%
Distal			21	23.9%
Diffuse			13	14.8%
TFV (ml)	2973–21,988	10,645	11.074 ± 4208	
VFV (ml)	1130–9297	3940	4213 ± 1777	
SFV (ml)	1843–14,347	6700	6885 ± 2780	
MRV (ml)	21.2–269.0	85.7	88.9 ± 44.3	

BMI body mass ındex, *TFV* total abdominal fat volume, *VFV* visceral fat volume, *SFV* subcutaneous fat volume, *MRV* mesorectal fat volume

Table 2 This table demonstrates the relationship between the MRV and certain values such as height, weight, BMI, TFV, VFV, and SFV

	MRV	
	r	p
Age(years)	−0.019	0.863
Height(cm)	0.226	*0.034*
Weight(kg)	0.393	*0.000*
BMI (kg/m^2)	0.366	*0.000*
TFV(ml)	0.484	*0.000*
VFV(ml)	0.666	*0.000*
SFV(ml)	0.341	*0.001*

Spearman correlation test; *BMI* body mass ındex, *TFV* total abdominal fat volume, *VFV* Visceral fat volume, *SFV* subcutaneous fat volume, *MRV* mesorectal fat volume

Table 3 The detailed values of all patients on the basis of the pathological response rates to nCRT

	No pathological response		Minimal pathological response		Near-complete pathological		Complete pathological	
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median
Age	64.9 ± 13.2	66	63.6 ± 11.7	63	61.4 ± 8.1	64	60.7 ± 9.9	60
Gender								
Male	10	35.70%	4	28.60%	11	40.70%	6	31.60%
Female	18	64.30%	10	71.40%	16	59.30%	13	68.40%
Height (cm)	165 ± 7.8	163	165.3 ± 5.2	165	163.7 ± 5.5	163	166.7 ± 7	167
Weight (kg)	69.7 ± 12.5	64.5	74 ± 9.2	75	71.9 ± 11.5	69	76.2 ± 12.2	79
BMI (kg/m^2)	25.6 ± 3.1	25.2	27.1 ± 2.9	27.4	26.8 ± 3.9	25.9	27.4 ± 3.9	27.9
T								
III	17	60.70%	10	71.40%	19	70.40%	13	68.40%
IV	11	39.30%	4	28.60%	8	29.60%	6	31.60%
N								
0	11	39.20%	4	28.60%	13	48.10%	14	73.70%
I	15	53.50%	7	50.00%	8	29.70%	4	21.10%
II	2	7.30%	3	21.40%	6	22.20%	1	5.20%
Location								
Proksim	10	35.70%	4	28.60%	6	22.20%	4	21.10%
Middle	10	35.70%	4	28.60%	10	37.10%	6	31.50%
Distal	3	10.70%	5	35.70%	5	18.50%	8	42.10%
Diffusely	5	17.90%	1	7.10%	6	22.20%	1	5.30%
TFV (ml)	9769 ± 3770	8773	11,617 ± 3637	10,313	11,088 ± 4413	10,566	12,579 ± 4615	13,257
VFV (ml)	3821 ± 1995	3402	4184 ± 1596	3993	4055 ± 1414	3741	5034 ± 1890	5205
SFV (ml)	5948 ± 2108	5229	7433 ± 2537	6445	7107 ± 3258	7127	7545 ± 2926	8480
MRV (ml)	68.9 ± 35.3	60.3	76.5 ± 28	64	88.5 ± 24.5	86.4	128 ± 61.8	123.3

BMI body mass index, *TFV* total abdominal fat volume, *VFV* visceral fat volume, *SFV* subcutaneous fat volume, *MRV* mesorectal fat volume

[AUC: 0.757 (0.653–0.842), $p < 0.001$] in receiver operating characteristic (ROC) curve analysis (Graphic 1).

No statistically significant association was found between the MRV values and the T stages of the disease, whereas it was shown a statistically significant negative relationship exists between MRV and tumor N stage ($p < 0.05$) (Table 5).

Discussion

Certain parameters are used for predicting the pathological response to neoadjuvant chemoradiotherapy. Studies indicate that early N stage and small tumor size, together with low CEA values, can be used as a parameter in the prediction of response to nCRT [18–20]. These parameters may occasionally lead to varying results; nevertheless, we have also other options in hand, for this prediction task including MRI sequences such as diffusion-weighted imaging (DWI), T2-weighted imaging (T2WI), and dynamic contrast MR imaging [21–23]. To the best of our knowledge, this is the first study to investigate the role of the mesorectal adipose tissue in the prediction of the pathological response to nCRT for the treatment of rectal cancer. A previous study

has focused on the effects of TFV, VFV, and SFV on the survival rate in rectal cancer patients [24]. Another study has revealed that the survival rates increase as the MRV increases [25]. In our study, however, we have investigated the effects of MRV on the response to nCRT in patients with rectal cancer.

The amount of mesorectal adipose tissue is more affected by foreign fat accumulation than the natural bone structure around the pelvis [25]. Therefore, as the total body fat increases, the mesorectal adipose tissue volume also increases. There is also a positive correlation between MRV and VFV, TFV, and SFV ($p < 0.05$). The correlation coefficient between MRV and VFV is rather high. This may well be attributed to the fact that MRV is a component of VFV. This positive correlation between the VFV and MRV has also been demonstrated in various previous studies [26]. A valuable result of our study was the increased response to nCRT at higher MRV values. Although our study has not aimed to investigate the possible effects of TFV, VFV, and SFV on the pathological response to nCRT, the study has shown that these factors do not affect the pathological response. However, Lee et al. [27] demonstrated that the subcutaneous and visceral adipose tissue volumes, MRV is a

Table 4 The detailed analysis of the data on the basis of the grouping of patients according to their pathological responses to nCRT, as response-negative and response-positive

	Pathological response (−)			Pathological response (+)			p
	Mean ± SD/n%		Median	Mean ± SD/n%		Median	
Age (years)	64.6 ± 12.7		66.0	61.1 ± 8.7		61.0	0.133[a]
Gender							
Male	14	34.1%		17	36.2%		0.843[c]
Female	27	65.9%		30	63.8%		
Height (cm)	164.9 ± 7.0		164.0	164.9 ± 6.2		165.0	0.966[a]
Weight (kg)	71.1 ± 11.7		67.0	73.6 ± 11.7		75.0	0.201[a]
BMI (kg/m^2)	26.1 ± 3.1		25.8	27.0 ± 3.9		26.7	0.326[a]
T							
III	26	63.4%		33	70.2%		0.499[c]
IV	15	36.6%		14	29.8%		
N							
0	14	34.1%		28	59.6%		***0.023***[c]
I	22	53.7%		12	25.5%		
II	5	12.2%		7	14.9%		
Location							
Proximal	14	34.1%		10	21.3%		0.266[c]
Middle	14	34.1%		16	34.0%		0.829[c]
Distal	7	17.1%		14	29.8%		0.252[c]
Diffuse	6	14.6%		7	14.9%		0.789[c]
TFV (ml)	10,410 ± 3829		9474	11,654 ± 4472		11,524	0.198[b]
VFV (ml)	3925 ± 1880		3724	4463 ± 1662		4150	0.054[b]
SFV (ml)	6485 ± 2352		6111	7233 ± 3088		7299	0.227[b]
MRV (ml)	69.6 ± 31.0		62.4	105.8 ± 47.5		103.7	***0.000***[b]

BMI body mass index, *TFV* total abdominal fat volume, *VFV* visceral fat volume, *SFV* subcutaneous fat volume, *MRV* mesorectal fat volume

[a]*t* test, [b]Mann–Whitney *U* test, [c]Chi-square test

component of VFV, have an effect on the survival of rectum cancer patients. We think that further studies are needed to investigate the effects of the visceral and subcutaneous fat volumes on the pathological response to nCRT.

No statistically significant association was found between the MRV and the T stages of the tumor. On the other hand, a negative correlation was found between the MRV and the N stage of the tumor: the MRV was found to decrease as the N stage increased ($p < 0.005$). Torkzad et al. [28] have shown that nodal involvement was less in patients with high mesorectal volumes, in a multinational study they performed on 267 rectal cancer patients. The fact that a high MRV is associated with a higher response rate to nCRT may be explained by the buffer effect of the fat compartment against the local invasion and intrafascial micro lymph-node-metastasis of the tumor [29, 30]. In other words, it may be said that as the N stage increases, the MRV decreases; and this gives way to an increase in tumor burden and decrease in response. On the other hand, it is possible that the N stage may have increased due to the initially low MRV present at the beginning of the disease. Both of these circumstances may cause this result. Another hypothesis we suggest to explain this situation is

that a local excretion of some forms of immune cytokines from the mesorectum due to the stimulation created by nCRT may be contributing to the effect of the therapy. Histopathological studies are needed to prove this hypothesis.

Our study has some limitations: (1) tumor sizes have not been taken into consideration. We consider that the tumor size may not have a large effect on the radiation dose. The presence of lymph nodes increases the radiation dose applied. Besides, in the presence of lymph nodes, radiation application is not focused on the tumoral area. All these factors led us to think that the tumor size may be neglected. Thus, a study has reported that tumor size is not a predictor of pathological response to nCRT [31]. (2) The single-center structure of our study is a limitation of its own. The number of our complete pathological-response patients is quite close to the numbers in the literature; but still, the rather low total number of our patients is a limiting factor in dividing them into two distinct groups, one with a full, and the other one with no, pathological response. This limitation is crucial in terms of statistical sample grouping. (3) There were also certain limitations on assessment and evaluation. The images we evaluated

Graphic 1 Receiver operating characteristic (ROC) curves of MRV for the prediction of the response to nCRT (*AUC* : area under the curve, *%95 CI* confidence interval). Cut-off values were determined by the Youden index
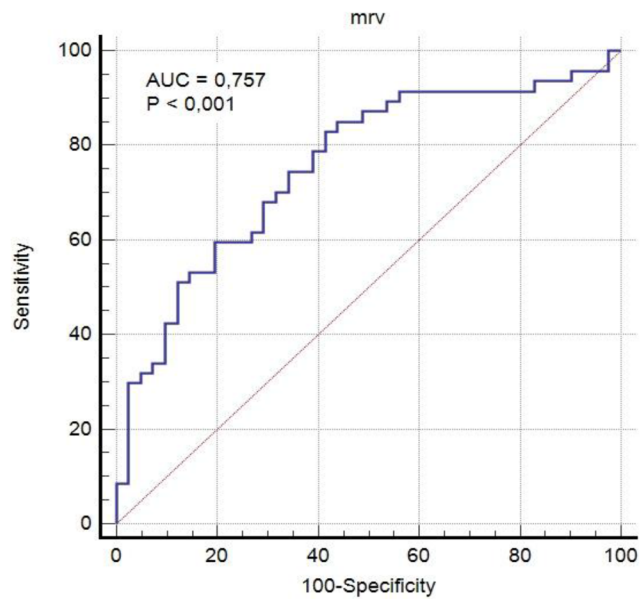
Variable	AUC(95%,CI)	Sensitivity	Specificity	Cut-off value	P value
MRV	0,757(0,653-0,842)	82,9	58,54	69,4	0<0,001

Table 5 The relationships between MRV and T-N stages

	Mezorectum volume			*p*
	Min–Max	Median	Mean ± SD	
T				
III	45.2–269.0	85.4	103.1 ± 57.1	0.273[b]
IV	21.2–148.7	85.9	81.9 ± 35.0	
N				
0	21.2–269.0	105.1	103.8 ± 52.0	*0.005*[a]
I	22.3–175.1	73.0	77.8 ± 32.0	
II	24.3–123.0	68.7	68.1 ± 26.1	

[a]Kruskal-wallis, [b]Mann–Whitney *U* test

were static, frozen images. This is rather intriguing, because it may lead to a false suggestion that the meso-rectum is an anatomically stable space and not influenced by the bodily habits of the individual [26]. Since there is no established reference point designated for the measurement of MRV, both the individual characteristics and the differences in experience of the evaluators may lead to false results. Thus, there is a certain need for standardization. In our study, evaluations were performed by two radiologists, utilizing the same reference points. We assume this has reduced the possibility of erring in measurements, to the minimums. These validations, however, need to be conducted within an interobserver structure.

Conclusions

Our study has demonstrated that MRV may be used as a novel parameter in predicting the pathological response to nCRT in patients with locally advanced rectum cancer. Routine MRV measurements may be performed easily on CT images of rectal cancer patients. It has been noted that the pathological response rate increases as the MRV exceeds 69.4 ml. The AUC value for MRV has been assessed as 0.757 (95% CI 0.653–0.842). We suggest that the fixation of the nutritional status of the patients could be of benefit for the final outcome of the therapy.

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