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Original Article

A pilot study: ensuring optimal adjustment for determinations of predictive values of preoperative investigations before starting a non-operative management protocol in locally advanced mid-distal rectal cancer

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Abstract: Purpose: Before starting a non-operative-management (NOM) protocol in locally advanced mid-distal rectal cancer, we have conducted a pilot study to find out the predictive value of our preoperative investigations. Methods: Between 2013 and 2017, 35 patients with locally advanced (cT3-4, N-any) primary mid-distal rectal adenocarcinoma were included in the study. We had two groups: Standard long-term chemoradiotherapy (CRT) (Group-1) and CRT + Consolidation chemotherapy (Group-2) groups. Both groups were evaluated regarding clinical (endoscopic-radiological) and pathologic response to neoadjuvant therapy. Each patient's d was prospectively recorded and findings were assessed according to NOM protocol and the clinical decisions recorded. The study was oriented to specify the predictive value of oncology team's hypothetical decisions in determining the right candidate for nonoperative management of rectal cancer. All patients underwent surgery with total mesorectal excision (TME) technique; thus, the hypothetical clinical decisions and pathologic results were compared. Results: The sensitivity and specificity of endoscopy were 57.1% and 87.5%; PPV was 80%, NPV was 70%, and accuracy was 73.3%. The sensitivity of MRI tumor regression grade scoring was 60%, specificity was 90%, PPV was 75%, NPV was 81.8%, and accuracy was 80%. The sensitivity and specificity of the final clinical decision were 80% and 90%; PPV was 80%, NPV was 90%, and accuracy was 86.6% in predicting proper management. Conclusion: An institutional adjustment for determinations of predictive values of preoperative investigations is beneficial before the start of nonoperative management protocol.

Keywords: Rectal cancer, organ-preserving, non-operative management

Introduction

The traditional curative approach of middle and distal rectal cancers for stage II and III (locally advanced) involves neoadjuvant chemoradiotherapy (CRT) followed by low anterior or abdominoperineal resection (APR) with total mesorectal excision (TME) technique and adjuvant chemotherapy [1, 2]. Surgical resection has been the mainstay treatment for many years in rectal cancer patients regardless of the response to neoadjuvant therapy. Although sphincter saving surgery became possible for many of patients with the help of new surgical techniques and preoperative radiotherapy's shrink effect, APR and the permanent stoma are still the only choices for tumors in the lowest 2 cm to 3 cm of the rectum that remains fixed to the levator muscles or anal sphincter.

Moreover, TME can lead to life-threatening complications such as anastomotic leakage, blood loss as well as some permanent problems such as bowel, bladder and sexual dysfunctions. The incidence of morbidity ranges from 6 to 35%, and the mortality rate reaches

up to 2% with TME [3]. The length of hospital admissions varies from 8 to 15 days [4, 5].

Over the last 15 years, there have been significant changes in the management protocols of rectal cancer. One of the most exciting development is non-operative-management (NOM) in patients who had neoadjuvant CRT followed by clinical complete (cCR) [6]. This new concept has been considering the possibility of avoiding planned major surgery after neoadjuvant treatment in patients with cCR. Literature data, which has reached a considerable amount of information and evidence, shows that organ preservative strategies can be taken into consideration especially in patients with distal rectal cancer.

Following neoadjuvant CRT remarkable rate (15-40%) of the patients had cCR with very low local recurrence (LR) rates and 5-year survival rates of greater than 95% [7, 8]. Patients who had cCR after neoadjuvant CRT can be determined by clinical, endoscopic and radiologically objective criteria [9]. The use of a NOM protocol in patients with a cCR would potentially spare patients from unnecessary surgical morbidity and result in excellent functional outcomes [6]. Before starting a NOM protocol in locally advanced mid and distal rectal cancer, we have conducted a pilot study to find out the predictive value of our preoperative investigations in terms of defining cCR (ycT0N0) comparing with pathological complete response (pCR) (ypT0N0) in the final histopathological verification.

Patients and methods

Study design

This is a retrospective analysis of prospectively recorded data. The protocol and study groups are given (**Figure 1**). NOM protocol (Group 2) has been adopted from Garcia Aguliar's study [10]. We used two different protocols that one group had standard long-term CRT without any chemotherapy in the waiting period before surgery (Group 1: Standart treatment protocol), the other had standard long-term CRT plus systemic chemotherapy (consolidation chemotherapy) in the waiting period before surgery (Group 2: Pilot study protocol). Both groups were evaluated in terms of clinical (endoscopic and radiological) and pathologic response to neoadjuvant therapy. In the Group-2 patients were assessed according to NOM protocol and the clinical decisions for each patient were prospectively recorded. All patients in Group 1 and Group 2 underwent surgery with the TME technique; therefore, we were able to crosscheck the clinical decision and pathologic results. All treatment methods were carried out following relevant guidelines and regulations. The local ethics committee approved the study. Informed consents were taken from all the participants. The study aimed to compare two groups consist of locally advanced rectal cancer treated with a different accepted international approach and simulated a hypothetical evaluation process by the oncology team. The decision-making process and final decisions were changed neither the patients' treatment protocol nor the time of surgery. The final hypothetical decisions on whether patients may follow up with the watch-and-wait protocol to spare them from surgery were made according to the clinical response criteria used for endoscopic and pelvic MRI. Surgery protocols the patients had undergone were a part of standard practice.

Between 2013 and 2017, 35 patients with locally advanced (cT3-4, N-any) primary rectal adenocarcinoma within 10 cm from the anal verge and eligible for neoadjuvant long-term CRT were included in the study. Exclusion criteria were as follows: early T stage (cT1-2, N-any), proximal tumors (>10 cm from anal verge), synchronous colorectal or other primary tumors, polyposis syndromes. A full colonoscopy was performed to obtain histopathologic diagnose and tumor location. The staging was carried out with thorax and abdominal computed tomography (CT) and or PET/CT. The local staging was performed by pelvic magnetic resonance imaging (MRI) with rectal cancer imaging protocol in all patients. Images were obtained by a 1.5-T or greater MRI with T2-weighted images, in an oblique plane, perpendicular to anal canal (would help examine the intersphincteric plane), in a coronal plane, parallel to the anal canal. For investigating lymph node involvement, three-millimeter slices parallel to sacrum images were obtained.

Study groups

Treatment protocols schemes (**Figure 1**).

Group 1 (Standard treatment protocol-long course CRT group): 20 patients who did not agree to take part in the pilot study protocol or

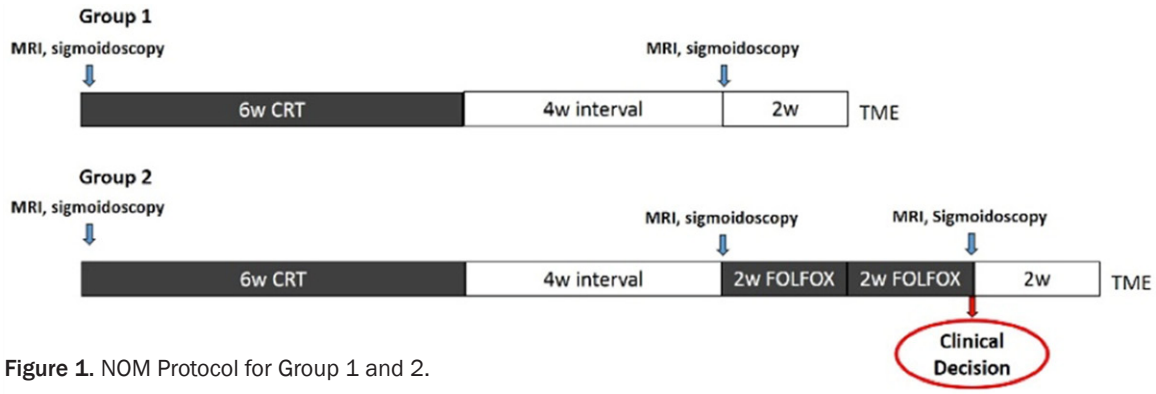


Figure 1. NOM Protocol for Group 1 and 2.

referred from another institution after completion of CRT were included in Group 1. The interval between neoadjuvant treatment and surgery was six weeks. All the patients received 50.4 Gy in 28 fractions pelvic radiotherapy and concomitant oral Capecitabin 825 mg/m^2/twice daily during radiotherapy. After 4 weeks, patients were re-evaluated by sigmoidoscopy and pelvic MRI. Patients underwent surgery (TME) 6 weeks after completion of CRT.

Group 2 (Pilot study group): 15 patients who agreed to take part in the pilot study protocol were included in Group 2. Tumor response was evaluated with sigmoidoscopy and pelvic MRI 4 weeks after completion of long-course CRT (same as Group 1). Afterward, two cycles consolidation chemotherapy of FOLFOX bi-weekly (Oxaliplatin 85 mg/m^2 and concomitant Leucovorin 400 mg/m^2 during 2 hours and right after bolus 5-Fluorouracil 400 mg/m^2. Later on, 46 hours 5-Fluorouracil infusion of 2400 mg/m^2) was given. Following consolidation chemotherapy, sigmoidoscopy and pelvic MRI were repeated and final clinical decision (whether cCR defined or not) was recorded prospectively. Two weeks after, surgery (TME) was performed independently of response to neoadjuvant treatment. The total interval between long-course CRT and TME was ten weeks in this group.

Assessment of clinical response (CR)

The clinical response criteria used for endoscopic and pelvic MRI were shown in **Table 1**. MRI evaluation was done in two ways: The first one was conventional evaluation and tumor regression grade (TRG). T and N staging of the tumor before and after treatment were evaluated. Assessment of the T stage was made between T0 and T4. For N staging, those with lymph node (LN) diameters greater than 5 mm were positive, while those below 5 mm were negative. In conventional evaluation, cases defined as T0, T1, and T2 with negative nodes were evaluated as cases compatible with organ preservation, and node-positive cases with T3 and T4 disease were evaluated as unfavorable cases for NOM. The second way was evaluating the response by MRI TRG scores. MRI TRG scores were assessed by dividing into the following five categories according to the assessment method described by MERCURY group [11]: Grade 1 Radiological complete response (linear/crescentic 1- to 2-mm scar in mucosa or submucosa only); Grade 2 Good response (dense fibrosis; no visible residual tumor, signifying minimal residual disease or no tumor); Grade 3 Moderate response (>50% fibrosis or mucin and visible intermediate signal); Grade 4 Slight response (little areas of fibrosis or mucin but mostly tumor); Grade 5 No response (intermediate signal intensity, same appearances as original tumor/tumor regrowth). If MRI-TRG was assessed as grade 1 or grade 2, cases were evaluated as appropriate for NOM. The grade 3 and above were evaluated as inappropriate cases. In the final clinical evaluation at the multidisciplinary team (MDT) meeting, we only considered MRI-TRG score evaluation instead of conventional MRI findings for the NOM decision.

The decision of MDT meeting: final clinical decision

After neoadjuvant treatment was completed, the treatment decisions were taken at the MDT meeting by colorectal cancer study group consisting of a colorectal surgeon, medical oncologist, radiation oncologist, radiologist, nuclear

Table 1. The Criteria of Clinical Response

	Complete Response	Near-complete Response	Incomplete Response
Endoscopy	Flat, White scar Telengiectasia No ulcer No nodularity	Irregular mucosa Small mucosal nodules or minor mucosal abnormality Superficial ulcer Mild persisting erythema of the scar	Visible tumor
MRI			
cT	T0	T1-2	T3-4
cN	N-	N-	N+
Tumor regression grade	1	2	3-5

Table 2. Demographic, clinical and surgical characteristics of the patients. SPS: Spincter preserving surgery, APR: Abdominoperineal resection

	Group 1 (n=20)	Group 2 (n=15)	p
Age (mean ± SD)	58.7±10.7	53.1±7.9	0.084
Gender (Male/Female)	9/11	6/9	0.521
Tumor site			0.272
Mid-rectum	4 (20%)	1 (6.7%)	
Distal rectum	16 (80%)	14 (93.3%)	
Clinical T stage			0.610
cT3	18 (90%)	14 (93.3%)	
cT4	2 (10%)	1 (6.7%)	
Clinical N stage			0.390
cN-	1 (5%)	2 (13.3%)	
cN+	19 (95%)	13 (86.7%)	
Clinical Stage			0.581
II	2 (10%)	2 (13.3%)	
III	18 (90%)	13 (86.7%)	
Surgery			0.419
SPS	17 (85%)	14 (93.3%)	
APR	3 (15%)	1 (6.7%)	
Technique			0.419
Laparoscopic	3 (15%)	1 (6.7%)	
Robotic	17 (85%)	14 (93.3%)	

medicine specialist, and pathologist. For this purpose, endoscopic and radiological response/regression criteria are defined in **Table 1** for each modality, and subgroups are constructed using these parameters as well as T stage, N stage, and MRI-TRG parameters. Final clinical decision (prediction) was made in the MDT meetings.

Patients who were assessed as a complete radiological response with MRI (MRI-TRG score 1) and near normal or flat mucosa without ulcer or nodularity at the endoscopy (endoscopic CR) were decided as NOM candidate.

Also, superficial induration with endoscopic mucosal abnormalities, N-disease at the MRI and patients with MRI-TRG 2 (NCR) was decided as local excision (LE) candidate with transanal endoscopic microsurgery (TEM) technique.

Digital rectal evaluation of palpable tumor nodules and endoscopically visible tumor, N+ disease at the MRI, patients with MRI-TRG 3 and above (ICR) were decided as suitable patients for surgery with TME.

The endoscopic and radiological data were compared with the detailed pathologic data after all patients underwent TME in the pilot study group (Group 2). Then the statistical predictive and accuracy ratios (positive predictive value-PPV, negative value-NPV) were determined for each modality.

Descriptions for predictive analyses

True positive: Clinical decision of TME (not eligible for NOM or LE) approved by pathologic examination.

True negative: Clinical decision of NOM or LE approved by pathologic examination.

False positive: Clinical decision of TME refuted by pathologic examination (i.e., preoperative TME decision in patients with pathologic complete response).

False negative: Clinical decision of NOM or LE refuted by pathologic examination (i.e. preoperative NOM decision in patients with pathologic alive tumor cells).

SPSS version 21.0 (SPSS, Cary, USA) was used for statistical analysis. Chi-square test and independence T-test were used for comparison of demographic, clinical and surgical character-

Table 3. Comparison of pathologic stages and tumor response between group 1 and 2. pCR: Pathologic complete response

	Group 1	Group 2	p
T stage			0.008
ypT0	1 (5%)	3 (20%)	
ypT1	0 (0%)	5 (33.3%)	
ypT2	6 (30%)	5 (33.3%)	
ypT3	11 (55%)	2 (13.3%)	
ypT4	2 (10%)	0 (0%)	
N stage			0.025
ypN0	12 (60%)	14 (93.3%)	
ypN1	3 (15%)	1 (6.7%)	
ypN2	5 (15%)	0 (0%)	
T downstaging	7 (35%)	14 (93.3%)	0.001
N downstaging	11 (57.9%)	12 (92.3%)	0.038
Downstaging	10 (50%)	14 (93.3%)	0.007
pCR	1 (5%)	3 (20%)	0.200
Mandard 1-2	6 (30%)	11 (73.3%)	0.013

Table 4. Association between T downstaging and N downstaging

		N downstaging		Total	p
		(-)	(+)		
T Downstaging	(-)	8	5	10	
	(+)	1	18	19	0.001
Total		9	23	32	

istics of the patients, for comparison of pathologic stages and tumor response between groups and association between T downstaging and N downstaging.

Surgery

Standard sharp TME was carried out in either laparoscopic or robotic surgery. Our technique of laparoscopic-TME has been described before [12].

Pathological evaluation

Macroscopic assessment and sampling: Procedures concerning mesorectal evaluation and sampling of the surgical specimens routinely used in our pathology laboratory were adapted from Quirke et al. [13] and Nagtegaal et al. [14].

Therapy response assessment

First of all, if the tumor regression findings were observed, their characteristics such as fibrosis, inflammation, calcification, and acellular mucin pool were noted. The viable tumor areas, tumor cell clusters, and isolated tumor cells were marked with colored pencil on the slide than those marked areas were copied onto their digital macroscopic images. If there was no any viable tumor even examining sections from the whole scarred area by using high power objective, serial sections, and if necessary, immunohistochemically pan-cytokeratin primary antibody was applied to the paraffin blocks including tumor scar to determine the pathological complete response. The extent of viable residual carcinoma at the primary site was assessed semi-quantitatively, based on the estimated percentage of viable residual carcinoma concerning the macroscopically identifiable tumor bed that was evaluated histologically. This percentage was recorded in the final pathology report of each case. Two different grading system was used for assessment of the histopathologic tumor regression degree. One of these is simple and reproducible grading systems for tumor regression described by Mandard et al. [15], and the other is Ryan scheme suggested by College of American Pathologist [16]. In each system, the score and explanation were reported.

Finally, the post-treatment pathologic TNM stage (ypTNM) was assessed [17].

Results

Demographic, clinical and surgical characteristics of Group 1 and 2 are shown in **Table 2**. All parameters were similar.

Tumor downstaging and CR

T downstaging was observed in 8 (40%) and 14 (93.3%) patients in group 1 and 2, respectively (p=0.001). N downstaging rate was also significantly higher in Group 2 when compared with Group 1 (92.3% vs 45%, p=0.003). Overall downstaging was seen in 9 (45%) patients in Group 1 and 11 (73.3%) patients in Group 2 (p=0.003). According to Mandard classification, 6 (17.1%) patients were Mandard 1, 11 (31.4%) patients were Mandard 2, 5 (14.3%) patients were Mandard 3 and 13 patients (37.1%) were Mandard 4. Superior tumor response (Mandard 1 and 2) scores were 6 (30%) in Group 1 and 11 (73.3%) in Group 2 (p=0.013). The pCR rate increased from 5% (1 patient in Group 1) to 20% (3 patients in Group

Table 5. Predictive analysis of preoperative staging methods and clinical decisions (organ preservation either NOM or LE, and surgery with TME) for Group 2 (pilot study)

Patient	Endoscopic prediction	Conventional MRI prediction	MRI tumor regression gradeprediction	MRI overall recommendation prediction	Final clinical decision/ prediction
1	TN	TN	TN	TN	NOM/TN
2	TN	TN	TN	TN	NOM/TN
3	TN	TN	TN	TN	NOM/TN
4	TN	TN	TN	TN	LE/TN
5	TN	TN	TN	TN	LE/TN
6	TN	TN	TN	TN	LE/TN
7	FN	FN	FN	FN	NOM/FN
8	FN	FP	TN	TN	LE/TN
9	TP	TP	TP	TP	TME/TP
10	TN	TN	TN	TN	LE/TN
11	TP	TP	TP	TP	TME/TP
12	FP	FP	FP	FP	TME/FP
13	FN	FP	TN	TN	LE/TN
14	TP	TP	TP	TP	TME/TP
15	TP	TP	FN	FN	TME/TP
Sensitivity	57.1%	80%	60%	60%	80%
Specificity	87.5%	70%	90%	90%	90%
PPV	80%	57.1%	75%	75%	80%
NPV	70%	87.5%	81.8%	81.8%	90%
Accuracy	73.3%	73.3%	80%	80%	86.6%

True negative, TP: True positive, FN: False negative, FP: False positive, PPV: Positive predictive value, NPV: Negative predictive value, TME: Total mesorectal excision, LE: Local excision, NOM: Non-operative management.

2) with consolidation chemotherapy but the dif 6 cases (40%) that we decided on LE with TEM (Group 2, Pt 4, 5, 6, 8, 10, 13). There were 5 cases (33.3%) with TME decision (Group 2, Pt 9, 11, 12, 14, 15) (**Table 5**).

When we evaluated the pathologic results (Pt 4, 5, 6, 10) we saw that we correctly identified TEM cases (**Figure 2**).

Most surprising patients with their investigations and pathologic data were presented in Figure-3 (Pt 7, 8, 12, 13, 15).

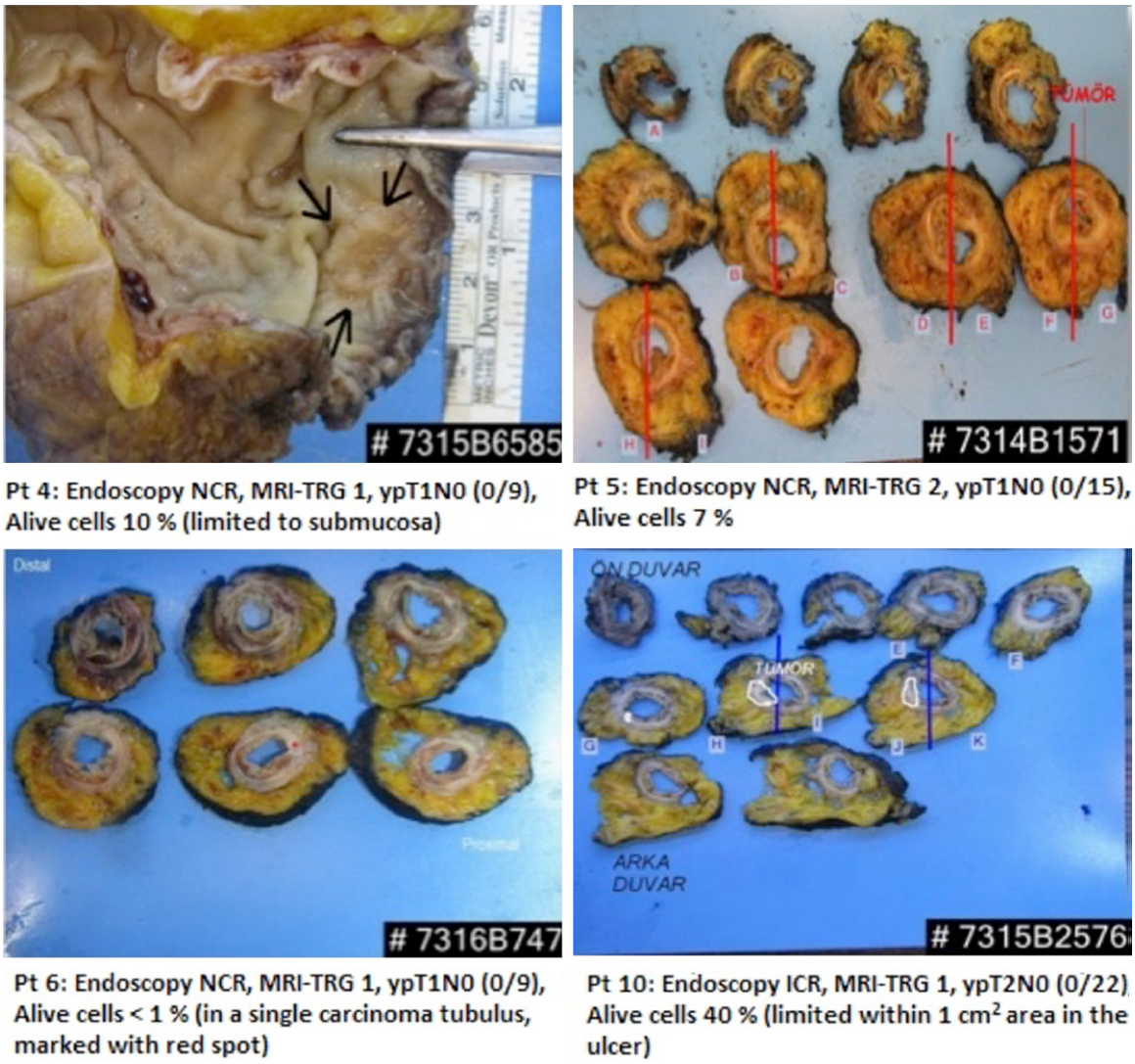
NOM candidates are shown (**Figure 4**).

Oncologic outcome in all patients

Mean follow-up was 37.97 (ranging 10-62) months for all patients. Local recurrence occurred in 2 patients (10%) in Group 1 and distant metastasis occurred in 4 patients in Group 1 (20%) and 2 patients in Group 2 (10%). In those 6 patients the metastasis was seen in lung in three patients, in peritoneum (peritoneal carcinomatosis) in two patients and in liver in one patient.

Discussion

One of the two major mechanisms for decision making procedure for NOM is the absence of the tumor on the wall, and the other is the negativity of lymph nodes. Endoscopy and MRI findings are important to define disappearing of the tumor in the wall. Based on the results of TME in Group 2, the accuracy of the preoperative evaluation results was 70% in determining complete response with endoscopy alone. Endoscopy evaluates only the lumen and it is insufficient in other wall layers. In some cases, very few cancer cells or submucosal alive cells lead to inadequate endoscopic evaluation (Group 2 pt 7, 8, 13, shown in **Figure 3**). In any layer of the intestinal wall of the residual tumor cells, the tumor can be seen independent of the state of the tumor and the presence of ulcer (Group 2 pt 12). There is a growing number of data with a similar conclusion in the literature [18-21].



Pt 4: Endoscopy NCR, MRI-TRG 1, ypT1N0 (0/9), Alive cells 10 % (limited to submucosa)

Pt 5: Endoscopy NCR, MRI-TRG 2, ypT1N0 (0/15), Alive cells 7 %

Pt 6: Endoscopy NCR, MRI-TRG 1, ypT1N0 (0/9), Alive cells < 1 % (in a single carcinoma tubulus, marked with red spot)

Pt 10: Endoscopy ICR, MRI-TRG 1, ypT2N0 (0/22) Alive cells 40 % (limited within 1 cm^2 area in the ulcer)

Figure 2. The correctly identified TEM candidates.

At the present daily practice, MRI is the most essential tool in the evaluation of non-luminal wall layers of choice, although similar limitations exist as in endoscopic results. In our study, the negative predictive value of MRI is 81.8%. That is, if the tumor seems to have disappeared from the wall in the MRI, it is straightforward. If the endoscopic appearance and MRI report that there is no tumor, these cases may be NOM candidates, with MDT decision (NPV 90%). Despite all the efforts, 10% of the cases may not end up with an accurate prediction. If there is the slightest doubt about NOM decision, or the patient's determination or compliance with the treatment, the decision should be radical surgery, instead of NOM. In a similar study evaluating MRI, endoscopy, and clinical decisions for NOM, the rate of clinical CR was 90% and MRI (T2A and DAG) 75% [22].

In our study the MR-TRG scores' specificity, PPV and accuracy were superior to the conventional MRI assessment on the T stage. Restaging with conventional MRI after CRT is insufficient because fibrosis-tumor differentiation is difficult and fibrosis is often misinterpreted as a residual tumor (Group 2, pt, 8, 12, 13 **Figure 3**). In literature, there are a few reports which show the efficacy of MR-TRG score assessment to show the pathological CR [23, 24]. Bhoday and colleagues showed that the sensitivity of MR-TRG score 1 to 3 to identify pCR was 94% (95% CI, 0.74-0.99) in their research [23]. Sclafani and colleagues stated in

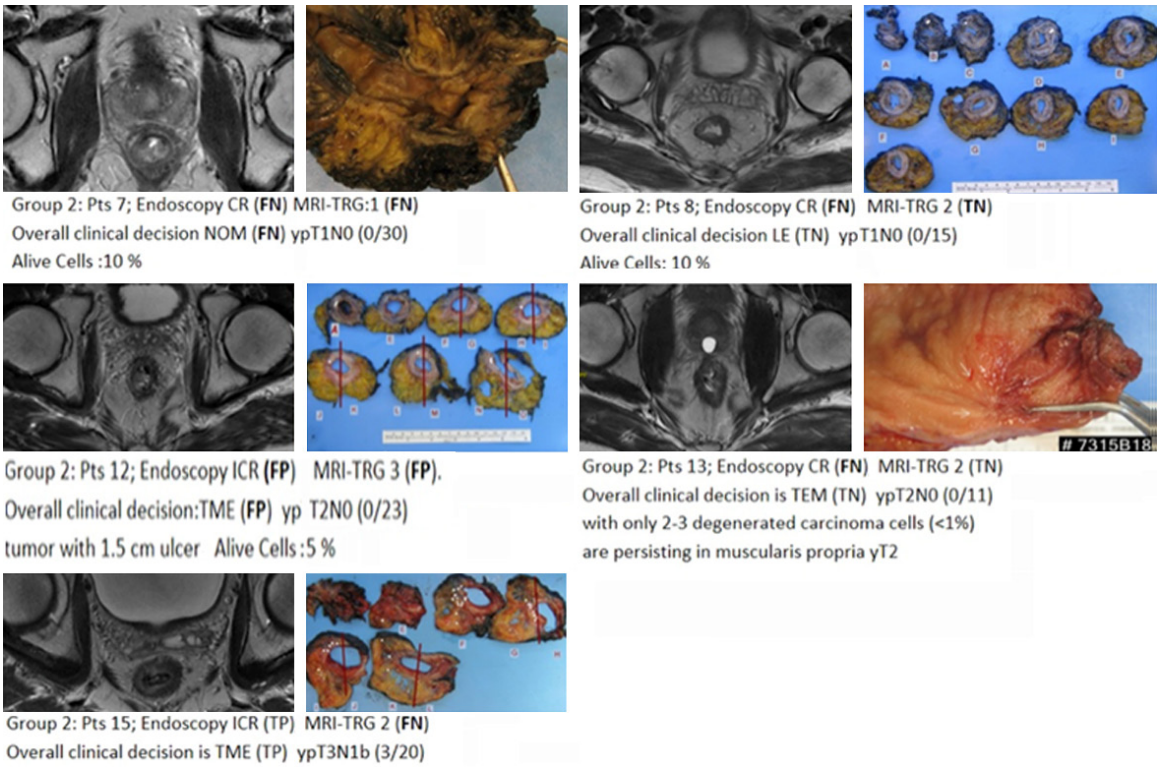


Figure 3. Pathologic data of problematic cases (FN, FP, TP, TN) (Pt 7, 8, 12, 13, 15) as a result of endoscopy, MR or MDT meeting evaluation. In Pt 7, after evaluation of MRI and endoscopy no tumors were not detected and decision was NOM, but the pathology was 10% live cell and YPT1NO (30/0). When we evaluated Pt 8 endoscopy was normal (white scar) but MRI-TRG score was grade II so the final decision was TEM instead of NOM. Pathology was ypT1N0 so even though endoscopy skipped final decision was right. In Pt 12, TME decision was made in MDT because of endoscopy ICR decision (1.5 cm ulcerous tumor) and MR-TRG SCORE III (incomplete). However, TEM could be performed with because of the pathology, ypT2NO, 1.5 cm ulcer and 5% viable cell. In Pt 13, despite the CR on endoscopy, MR-TRG SCORE was III (incomplete) and MDT decision was TEM; pathologically end-stage YPT2NO with a viable cell ratio of less than 1% and localized to the muscularispropria. In this case endoscopy was wrong. On Pt 15, the endoscopic response was ICR and the MRI-TRG score was 3 but N+ for the 8 mm lymph node. The MDT decision was TME and the pathology result was ypT3N1b. In this case, 8 mm lymph nodes were negative but other three lymph node which were reported as positive the largest 0.3 mm in diameter and MRI could not evaluate them On Pt 15, the endoscopic response was ICR and the MRI-TRG score was 3, lymph node recorded as N+ according to the 8 mm diameter. The MDT decision was TME because of suspected lymph node. The pathology result (ypT3N1b) seemed comtetible with MDT decision. But, It was a good decision that was made for the wrong reason, because the radiologically suspected lymph node was negative and there was three pathologic lymph node with the largest 0.3 mm in diameter that MRI could not point them.

their study that the sensitivity and specificity of MR-TRG scores 1 and 2 (complete/good radiological regression) for the prediction of pathological complete response was 74.4% (95% CI: 58.8-86.5) and 62.8% (95% CI: 54.5-70.6), respectively [24]. They also assessed the agreement between MR-TRG and pathological TRG (pTRG) and stated that the agreement between mrTRG and pTRG is low and mrTRG cannot be used as a surrogate of pTRG. Nevertheless, they have mentioned that given the ability to provide a non-invasive assessment of tumor response, mrTRG remains a potential tool for the implementation of neoadjuvant treatment strategies following standard chemo-radiotherapy including deferral of surgery/watch and wait or further (i.e., sequential/salvage) therapy [24]. In our study, the sensitivity of MRI tumor regression grade scoring was 60%, specificity was 90%, PPV was 75%, NPV was 81.8% and accuracy was 80%.

What we have discussed so far is the treatment decisions in the patient group, which we assume that the lymph node (LN) is negative. Clinically, LN should be negative. However, in the literature, the size of positive LN has been reported as less than 5 mm, in 30-50% of

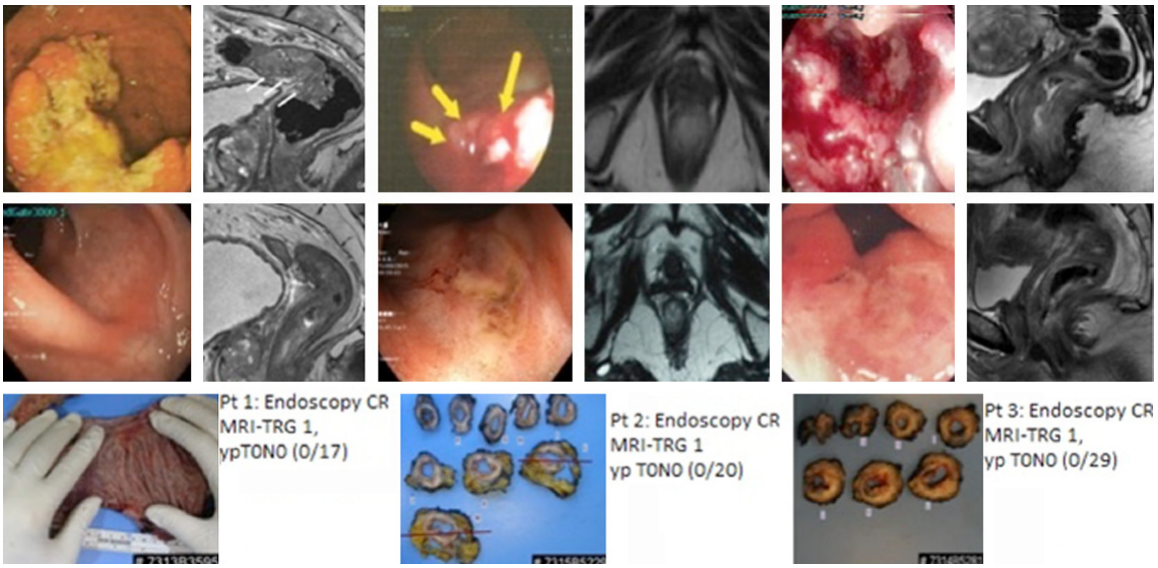


Figure 4. The correctly identified NOM candidates.

cases. This suggests that the currently accepted 5 mm threshold value for LN evaluation is an inadequate criterion for determining LN positivity [25, 26]. The direct identification of MRI LN status is still limited. In our study group, 94.2% of the 35 cT3, four patients in group 1 and 2 were diagnosed as having positive lymph node. This ratio is 95% in group 1 and 93.3% in group 2. After neoadjuvant treatment, ypN (+) 40% in group 1 and 6% in group 2. When the waiting time is prolonged and chemotherapy is added, better outcome can be obtained. The joint decision of the MRI and endoscopy to tumoral lesions status on the wall may increase the accuracy of the positive-negative decision given in the fact that current clinical practices do not depend only on the diameter of the LN. If there is a deletion on the wall in both assessments, the likelihood of positive lymph nodes is significantly reduced. Evaluating these parameters might be more sensitive than the dimension criterion.

The predictive model that includes molecular markers and MRI imaging may not be the best clinical utility at this point in time. Predictive modeling may be more valuable with a particular type of functional imaging such as positron emission tomography (PET) 18-Fluorodeoxyglucose (FDG) PET-computed tomography (CT) that detects and quantifies increases in glucose metabolism within cancer cells [27]. The molecular mechanism underlying the detection of rectal cancers by 18-FDG PET-CT has primarily shown that the specific biological characteristics of cancer, such as tumor size, cell density, invasion, and hypoxia, determine its glucose metabolism. Also according to Shihara et al. with the use of re-evaluation of tumor response to the treatment, using PET-CT can provide a compelling data to predict the presence of residual lateral node metastases after neoadjuvant chemoradiotherapy (n-CRT). Using size and metabolic estimate (maximum standardized uptake value (SUV max)) cut-offs after n-CRT, they were able to predict with high accuracy the presence of lateral node metastasis [28].

This approach enabled the researchers to accurately identify the patients that could benefit the most from lateral lymph node dissection.

A combination of data from all imaging modalities will improve the predictive specificity of the CRT response [29], expanding the opportunities to preserve organs. A combination of many variables including clinical, pathological, imaging, proteomic, and genomic factors, and blood biomarkers, is required to develop a robust pre-treatment predictive model. Different tumor behaviors are likely attributable to the many interactions among multiple factors.

The most important limitation of the present study is the relatively small sample size, and

thus some of the interpretation of the results is required. Another limitation of our assessment is that we did not include the diagnostic performance of the diffusion-weighted magnetic resonance imaging (DW-MRI) which has been reported that might be a contribution to fibrosis-tumor differentiation. The addition of DW-MRI sequences could increase our sensitivity. However, this sequence has not been used in our study design (in some of the cases they were not obtained, while in other cases they were suboptimal due to artifacts).

In conclusion, endoscopic and radiological findings are significant in determining the right candidate for non-operative management of rectal cancer. The clinical decisions should be taken in the multi-disciplinary team meetings because of the necessity of individualization of therapy as well as having experience of endoscopist and radiologist. Therefore, an institutional adjustment for determinations of predictive values of preoperative investigations is beneficial before the start of nonoperative management protocol.

Disclosure of conflict of interest

None.

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