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The impact of total neo-adjuvant treatment on nonoperative management in patients with locally advanced rectal cancer: The evaluation of 66 cases

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ABSTRACT

Background: The study aimed to assess if adherence to a total-neoadjuvant-treatment (TNT) protocol followed by observation(watch-and-wait) led to the successful nonoperative-management of low-rectal-cancer.

Methods: In this study, patients with primary, resectable-T3-T4, N0–N1 distal-rectal-adenocarcinoma underwent-chemoradiotherapy + consolidation-chemotherapy (TNT). During the-TNT-period, endoscopy, MRI, and FDG-PET/CT were performed. We allocated patients with complete-clinical-tumor-regression, who underwent endoscopy every two months, MRI every-four-months, and PET/CT every-six-months-after-treatment, to the observation-group(OG). All other patients were referred for surgery. The OG was followed-up. The primary endpoint was local tumor-ecurrence after allocation to the OG.

Results: Between 2015 and 2018, we enrolled 66-patients. Of 60-patients who were eligible to participate, 39 had complete-clinical-response(cCR) and were allocated to the OG, six underwent local-excision (LE), and 15 underwent total-mesorectal-excision (TME). The median follow-up duration was 22 (9–42) months. The local-recurrence-rate in the OG was 15.3%, and the LE and TME rates were 16.6% and 0%, respectively. All recurrence cases were salvaged through either LE or TME. The-distant-metastasis rate was 5.1%, 16.6%, and 12.5% in the OG, LE, and TME groups, respectively. The endoscopic negative-predictive-value(NPV) was 50%, and the positive-predictive-value(PPV) was 76.9% in the surgery group (LE + TME). MRI; NPV-50%, PPV-76.9%. PET/CT; NPV-100%, PPV-93.3%. Six patients(28.57%) from surgery group achieved complete pathological response (cPR).

Conclusion: Our results indicated a high proportion of selected-rectal-cancers with-cCR after neo-adjuvant-therapy could potentially be managed non-operatively, and major surgery may be avoided.

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Introduction

TME is the gold standard in the treatment of patients with non-metastatic rectal cancer [1]. While stage I disease is generally treated with surgery alone, the standard treatment for stage II and III rectal cancer involves neoadjuvant-chemoradiotherapy (nCRT) followed by TME and adjuvant-chemotherapy (aCT) [1].

Despite being associated with a high success rate, TME can lead to life-threatening complications such as anastomotic leakage, blood loss, bowel, bladder and sexual dysfunction, and perioperative mortality. The TME-related morbidity value ranges from 6 to 35% in the literature, while the corresponding mortality value is 2% [1–3]. In the last 15 years, there have been significant changes in the management of rectal cancer. With the use of nCRT and TME, a significant percentage (15–40%) of patients have had a complete pathological response (ypT0N0) with very low local recurrence rates, with 5-year survival rates higher than 95%. One of the most exciting developments is the "watch and wait" policy for patients treated with nCRT who show cCR. Preliminary studies have shown that the use of planned TME can be avoided after neoadjuvant-treatment in such patients [4]. Growing evidence in the literature indicates that the use of NOM could potentially decrease surgical morbidity and lead to excellent functional outcomes. [5].

To reach ultimate goal which is to accomplish pCR, the new concept include radiation dose escalation, adding of neoadjuvant-treatment with induction or consolidation-chemotherapy, and delaying the time of assessing tumor response after completion of neoadjuvant-therapy. Nevertheless, the long term effects of treatment approach on tumor response and long-term survival results are still controversial. [6–11].

Material-and-methods

Between 2015 and 2018, a total of 66 (40-male/26female) patients with LARC (cT3-4, N-any) primary rectal adenocarcinoma that was located within 10 cm from the anal-verge and who were eligible for long-term nCRT were included in the study. Exclusion-criteria were the presence of: early-T-stage (cT1-2, N-any) tumors, proximal-tumors (>10 cm from the anal verge), synchronous colorectal or other primary tumors, and polyposis syndrome. In the study, retrospective analysis of the patients was made by approval from the local Institutional-Review-Board (2019-02/4).

A full colonoscopy was performed for histopathologic diagnosis and to obtain data on tumor location. Whole-body-staging was performed using PET/CT. The locoregional staging was performed by pelvic MRI with a special rectal cancer imaging protocol in all patients.

A TNT was applied to all patients (Fig. 1). All patients were treated with image-guided intensity-modulated radiotherapy or volumetric intensity-modulated arc treatment using 6–10 MV photons. Patients received pelvic radiotherapy dose of 50.4/Gy delivered in 28-fractions and concomitant oral capecitabin 825 mg/m^2/twice daily during radiotherapy. After four weeks, all patients were reevaluated by sigmoidoscopy and pelvic-MRI. TNT was administered to those who achieved a cCR greater than 50%. Until June 2018, six cycles of consolidation chemotherapy were administered, comprising bi-weekly FOLFOX administration (oxaliplatin-[85 mg/m^2] and concomitant leucovorin-[400 mg/m^2] for two hours followed by a bolus injection of 5-fluorouracil [400 mg/m^2]; then, 5-fluorouracil-[2400 mg/m^2] was infused over 46 h) after CRT (49/60 patients). After June 2018 [12], the consolidation chemotherapy regimen was changed to: oxaliplatin-[130 mg/m^2] on day 1 plus capecitabine-[1000 mg/m^2] twice daily on days 1–14, every three/weeks for eight cycles (11/60 patients). During the study, all response evaluations were performed by endoscopy, MRI and PET/CT. Following consolidation-chemotherapy, sigmoidoscopy, pelvic-MRI and PET/CT were repeated, and the final clinical decision on cCR presence was made, and this was recorded prospectively.

Post-chemoradiotherapy evaluation

Endoscopy

The cCR-criteria were taken from the endoscopic-criteria suggested by Habr-Gama et al. [13].

MRI Tumor Regression Grade score, as defined by the MERCURY group, and additionally high b-value (b1000) diffusion-weighted MRI sequences were evaluated and included in the findings by the radiologist.

The [18F]FDG-PET/CT images were reviewed for abnormal FDG uptake in the primary tumor, LNs, and distant sites. PET/CT images were compared with primary tumor activity, background activity and compared in every study stage with those in all the previous images.

The decision to watch and wait

After neoadjuvant-treatment was completed, treatment decisions were taken at the multidisciplinary-team meeting. The clinical-response-criteria used for endoscopy, MRI and PET/CT are shown in (Table 1).

If the findings were not compatible with cCR in any of the aforementioned three evaluation methods, the patient was referred for surgery. During TNT administration, if any signs of clinical tumor progression were observed either by endoscopy or imaging, the patient underwent TME.

Follow-up

NOM and TME groups: Patients were followed-up by endoscopy and digital rectal examination (DRE) every two months and the levels of carcinoembryonic antigen (CEA) and CA 19-9 were measured every three months for five years. MRI was performed every four months and PET/CT every six months, and all tests were repeated at the first, third and fifth years thereafter. At each follow-up, the patients' findings were compared to their previous recorded endoscopy, MRI and PET/CT findings.

LE group: To facilitate locoregional monitoring, baseline MRI and endoscopy were performed at four weeks, postoperatively, in this group. Patients were followed-up by endoscopy and DRE every two-months, CEA and CA 19-9 levels were measured every three-months, MRI was performed every four-months, PET/CT was conducted every six-months, and colonoscopy was performed at the first, third and sixth years thereafter.

Statistics

SPSS for Windows v22.0 (IBM, IL, USA) was used for all analyses. Variables were expressed as means and standard deviation, and as frequency and percentages. The associations between categorical variables were tested with a chi-square test, while those between continuous variables were tested by an independent samples *t*-test. The associations between non-parametric variables were tested by a Mann–Whitney *U* test, and p values < 0.05 were considered statistically significant.

Results

A total of 66 patients with LARC were treated within the TNT protocol between 2015 and 2018. Six patients were excluded from the evaluation for the following reasons: two patients developed

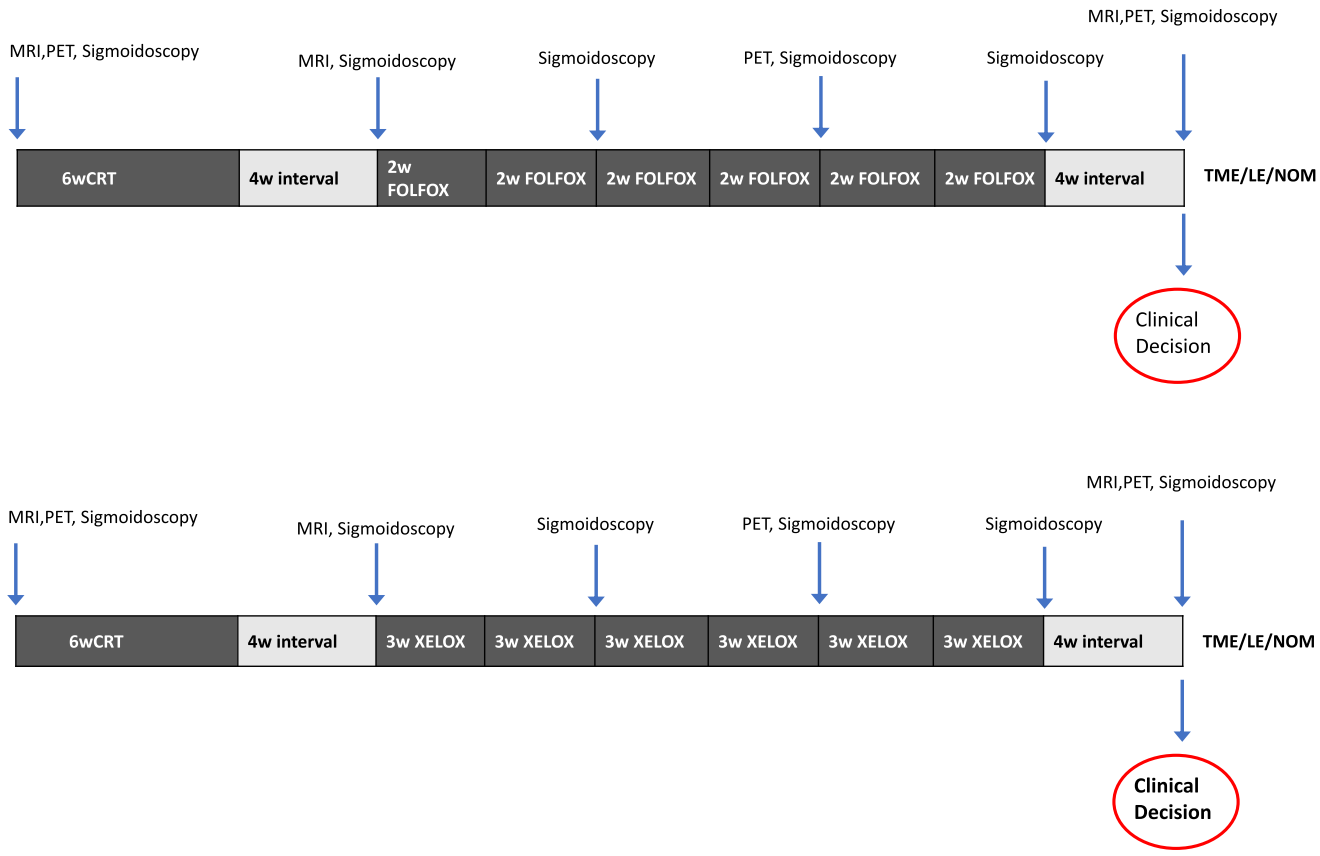

Fig. 1. Study protocol.

Table 1
Clinical response criteria.

Clinical Response Criteria			
Endoscopy	Complete Response	Near-complete Response/Incomplete Response	
		NC	IC
	- Flat, White scar - Telangiectasia - No ulcer - No nodularity	- Irregular mucosa - Small mucosal nodules or minor mucosal abnormality - Superficial ulcer - Mild persisting erythema of the scar	- Visible tumor
MRI			
	Complete Response	Near-complete Response/Incomplete Response	
MRI-Tumor Regression Grade Score	1,2	3,4,5	
DWI	−	+	
LN/TD	−	+	
PET/CT			
	Complete Response	Near-complete Response/Incomplete Response	
Metabolic Response	Absence of visual abnormal FDG uptake	Abnormal FDG uptake	

distant-metastasis (DM) (one in the paraaortic LNs and one in the liver) during TNT, and one patient developed myocardial infarction that was resolved with the placement of a coronary stent during TNT and who later underwent TME that revealed ypT2N0. Another patient was unable to tolerate further chemotherapy due to liver toxicity. In two patients, the characteristics of the tumor on endoscopy have changed through growing from a small ulcerative lesion to a bigger ulcerovegetative mass, concordant with local progression, during consolidation chemotherapy. Therefore, chemotherapy was resumed, and TME was performed, which revealed the presence of ypT2N0 and ypT3N0, respectively. These six patients not included to any further analyses.

NOM was achieved in 39 (65%) of the 60 patients (Fig. 2). The NOM group comprised LARC patients in whom cCR was achieved, who were then managed nonoperatively by mutual consent between the patient and the surgeon. Details on these cases are provided in Table 2. A total of 21 of the 60 (35%) patients underwent surgery. Six (10%) patients underwent LE, and 15 (25%) underwent TME (Table 3).

All the patients' tumor and treatment parameters were subject to univariate analyses, as summarized in Table 2. We did not observe a statistically significant relevance between initial T stage of the tumor and the cCR (p: 0.084) status, although the cCR rate was significantly increased in patients with clinical N (−), and

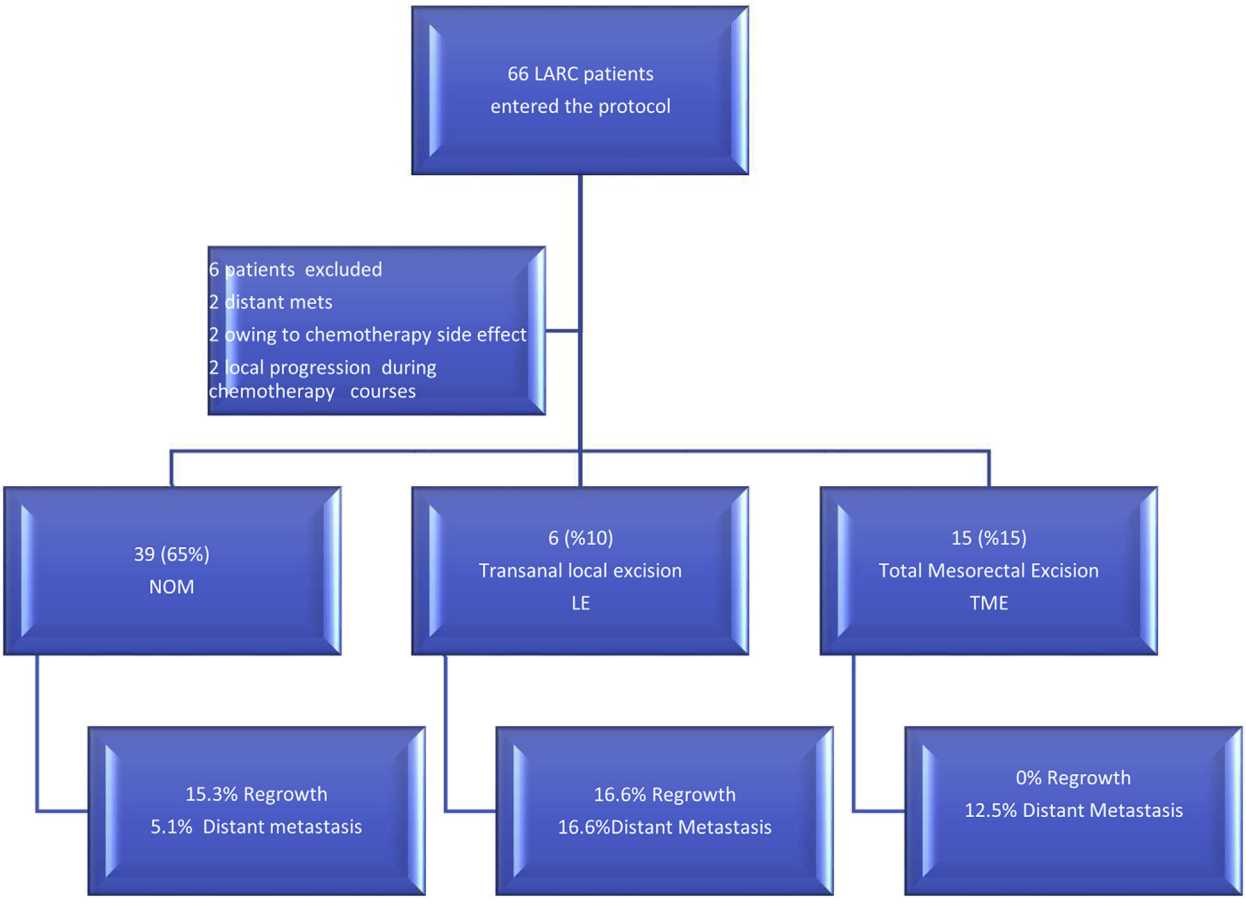

Fig. 2. LARC, locally advanced rectal cancer; NOM, Non Operative Management; LE, local excision; TME, total mesorectal excision.

extramural venous invasion (EMVI) (−) (p: 0.025, p: 0.023) (Table 2). The local staging of the tumor, based on MRI, was divided into the three groups: good, intermediate + bad, and ugly, based on the terminology used in a previous report [14], and there was a statistically significant difference between the groups in terms of the total cCR rate (p: 0.033).

A total of 45 (75%) patients showed a complete metabolic-response on PET/CT (39 in the NOM group, two in the LE group, and three in the TME group). Endoscopic cCR was achieved after 12 weeks of a waiting period in 21 (53.84%) of the patients. According to the initial work-up, an indication for abdominoperineal resection (APR) was observed in 31 (51,6%) of the patients. The APR indication rates were 70.90% in the NOM group, 9.67% in the LE group and 19.35% in the TME group.

Patients were evaluated retrospectively for wall and LNs and/or TDs according to the pathology results. The endoscopic NPV was 50% and PPV was 76.9% in both groups (LE and TME). The MRI NPV was 50% and PPV was 76.9%, while the PET/CT NPV was 100% and PPV was 93.3% (Table 4).

In keeping with the pathological findings, ypT0 was observed in four patients (44.44%). In one patient with ypT0N0, the TME decision was made due to an MRI TRG of 2, diff (−) but the LN was radiologically positive (6 mm) although PET/CT finding was the wall and LN cCR and also endoscopy had cCR. In two other patients with ypT0N0, although cCR was found to be achieved on MRI and PET/CT, surgery was performed in one due to the presence of stricture; the other patient was defined as having an incomplete clinical response, due to ulcer presence on endoscopic evaluation. A fourth patient with ypT0 was found to have achieved cCR according to endoscopy and PET/CT results, but LE was performed due to an MRI TRG score of 3 (mucin pool).

Fourteen patients underwent surgery owing to incomplete clinical response on endoscopy. Three patients (21.42%) had ypT0 disease. In one patient, TME was performed because of the presence of mesorectal TD-positivity on both MRI and PET/CT. On pathological examination, the disease type was found to be ypT0N1c. Two other patients with ypT0 (defined pathologically) underwent LE due to an MRI-TRG-score-of-3 (MRI-diffusion-negative), despite the achievement of cCR on PET/CT. LN evaluation was performed only in the TME group. The NPV on MRI was 87.5% and PPV was 71.4%, while on PET/CT the NPV was 100% and PPV was 100%.

Of those in the TME group, six had cT3b, three had cT3c, one had cT3d, and five had cT4 disease; the disease type in all cases was cN (+). Pathologic specimen examination revealed ypT0N0 presence in three cases; TD N1a LN-positivity in three cases; and ypN1b, ypN2, and ypN1c presence in one case each. In seven (46.6%) cases, fewer than 1% of live tumor cells were reported. In the LE group, four (66.6%) of the six patients had a live cell proportion lower than 1%. cPR was observed in six patients (28.57%) in the group which includes the patients underwent surgery, three (60%) in the LE group and three (20%) in the TME group.

All patients underwent sphincter-saving surgery, and inter-sphincteric resection + coloanal anastomosis was performed in seven (46.6%) patients in the TME group. Wound detachment was observed in three (50%) of the six patients who underwent LE, while subclinical anastomotic leakage occurred in four (26.6%) of the 15 patients who underwent TME; endoscopy was performed 10 days after surgery.

Table 2
Tumor stage and treatment parameters univariate analyses.

	n = 60	LE	NOM	TME	p
cT stage					0.084
T3a	10 (16.7%)	2 (20%)	8 (80%)	0	
T3b	22 (36.7%)	1 (4.5%)	15 (68.2%)	6 (27.3%)	
T3c	9 (15%)	0	6 (66.7%)	3 (33.3%)	
T3d	2 (3.3%)	1 (50%)	0	1 (50%)	
T4	17 (28.3%)	2 (11.8%)	10 (58.8%)	5 (29.4%)	
cN stage					0.025
cN-	11 (18.3%)	2 (18.2%)	9 (81.8%)	0	
cN+	49 (81.7%)	4 (8.2%)	30 (61.2%)	15 (30.6%)	
cTN stage					
cT3	43				0.029
cT3N-	10 (23.3%)	2 (20%)	8 (80%)	0	
cT3N+	33 (76.7%)	2 (6.1%)	21 (63.6%)	10 (30.3%)	
cT4	17				0.689
cT4N-	1 (1.6%)	0	1 (100%)	0	
cT4N+	16 (25.8%)	2 (12.5%)	9 (56.3%)	5 (31.3%)	
cCRM					0.166
cCRM-	24 (40%)	3 (12.5%)	18 (75%)	3 (12.5%)	
cCRM+	36 (60%)	3 (8.3%)	21 (58.3%)	12 (33.3%)	
cEMVI					0.023
cEMVI-	41 (68.3%)	4 (9.8%)	31 (75.6%)	7 (14.6%)	
cEMVI+	19 (31.7%)	2 (10.5%)	8 (42.1%)	9 (47.4%)	
cEMR LN					0.125
cEMR LN-	46 (76.7%)	6 (13%)	30 (65.2%)	10 (21.7%)	
cEMR LN+	14 (23.3%)	0	9 (64.3%)	5 (35.7%)	
Tumor					0.033
Very early	0	0	0	0	
Good	4 (6.7%)	1 (25%)	3 (75%)	0	
Bad/Intermediate	16 (26.7%)	2 (12.5%)	12 (75%)	2 (12.5%)	
Ugly	41 (66.7%)	3 (7.5%)	24 (60%)	13 (32.5%)	
Initial APR indication	31 (51.6%)	9.67%	70.90%	19.35%	
Chemotherapy protocol					
Xelox	11 (18.33%)	2 (3.3%)	8 (13.3%)	1 (1.66%)	
Folfox	49 (81.66)	6 (10%)	25 (41,6)	18 (30%)	

Oncological results

Watch-and-wait group

The median follow-up duration was 22 (9–42) months in this group. The six patients of (15.38%) NOM group had regrowth, all were salvageable (3 of them had TME, and 3 of them LE and one of them had additional brachytherapy). The time to regrowth was 35 months in one patient (ypT3N2a) and ten months in two others (ypT2N0 and ypT2N0). LE was performed in three patients, the first one at the 11 months (ypT2), the second one in 17 months (yPT3), the last one 8. Month (ypT2).

DM was detected in a total of two patients (5.1%). In one patient, bone metastasis was detected at the fourteenth month, and in another, lung metastasis in the eighth month.

At month 30, liver metastasis was observed in one patient on PET/CT in the standard follow-up protocol; the patient underwent metastasectomy, and the final pathology report indicated the presence of parasitic inflammation.

TME group

DM developed in two patients DM developed in two patients. ((12,5%), both-in-lung, at the-first (ypT3N2b) at 13th-month, second-patient (ypT2N1a) at 14th-month)).

LE group

DM was detected in one (16.6%) patient at month 23, and lung metastasectomy was performed. After eight months, local recurrence was detected in one patient (16.6%) who then underwent intersphincteric TME (rypT3N1) as a salvage surgery with the initial rpT3 pathology.

Discussion

It is known that systemic therapy (induction or consolidation chemotherapy) is the preferred treatment method for patients with high-risk disease, and TNT appears to effectively improve the rates of local control and disease-free survival. [15–17]. In this study, we evaluated the usefulness of the addition of consolidation therapy to standard chemotherapy in patients with distal rectal cancer. We found that cCR was achieved in 65% of the patients who were included in the watch-and-wait protocol. Five percent of the patients who underwent organ-sparing surgery (LE) achieved complete pathological (pCR) response. The total rate of pCR in those who eventually underwent surgery due to an inability to achieve cCR was 28.5%.

In the literature, the reported cCR rates are between 26.8% and 78% [18–24]) The wide variability in these values can be attributed to varying patient selection procedures, inclusion of small groups and early-stage disease cases, different CRT protocols, and extension of the waiting period by the addition of consolidation chemotherapy. [25]. Habr-Gama et al. also showed that the rates of cCR increased from 27% to 57% by the addition of consolidation chemotherapy to nCRT for distal rectal cancer [26].

Also recent data from Champalimaud Foundation [27], which reported from a prospectively maintained database selectively treated with neoadjuvant RT (45–50.4 Gy and 25 Gy) only in consecutive patients with moderate or high risk features for local recurrence on MRI. Patients achieved a cCR after CRT in 63% of cases.

In our study, we also noticed FDG-PET/CT total neoadjuvant-treatment was the most reliable modality of cCR and pCR for

Table 3
MRI, magnetic resonance imaging; PET, Positron Emission Tomography; CT, computed tomography; TRG, tumor regression grade; LN, lymph node; TD, tumor deposit.

First cTNM	TUMOR CLASSIFICATION	Last MR-TRG-SCORE	Last MR Diffision	Last MR LN/TD	Endoscopy Feature	Endoscopy	REASON							CLINICAL DESICION CHANGED DUE TO PET-CT	pTNM	CAP alive cell perc.	OP
							MR-WALL	MR LN/TD	OVERALL MRI-DESICION	PET-CT WALL	PET/CT LN/TD	OVERALL-PET-CT DESICION	OVERALL DESICION				
T3b, N(+), CRM(+) EMVI(−) EMR(+)	Ugly	2	(−)	(+)	White scar + telangiektasia	c(TN)	TN	FP	FP	TN	TN	TN	FP	Y	ypT0N0	0	TME
T3b, N(+), CRM(+), EMVI(+), EMR(−)	Ugly	4	(+)	−	ulcer	İc (TP)	TP	TN	TP	TP	TN	TP	TP	N	ypT3N0	60%	TME
T3b, N(+), CRM(+), EMVI(+) EMR(+)	Ugly	3	(−)	−	ulcer	İc (TP)	TP	FN	TP	TP	TP	TP	TP	N	ypT3N1b	<%1	TME
T3b, N(+), CRM(−), EMVI(−), EMR(−)	Intermediate	3	(−)	−	ulcer	İc (TP)	TP	TN	TP	TP	TN	TP	TP	N	ypT1N0	1%	TME
T3b, N(+), CRM(+), EMVI(+), EMR(+)	Ugly	2	(−)	(+)	ulcer	İc (TP)	FN	TP	TP	TP	TN	TP	TP	N	ypT3N2	20%	TME
T3b, N(+), CRM(+), EMVI(−), EMR(−)	Ugly	2	(−)	−	Whitite scar + stricture	C (TN)	TN	TN	TN	TN	TN	TN	TN	N	ypT0N0	0	TME
T3c, N(+), CRM(+), EMVI(+), EMR(−)	Ugly	2	Insufficent	(+)	White scar	C (TN)	TN	TP	TP	TN	TP	TP	TP	N	ypT0N1cM-	0	TME
T3c, N(+), CRM(−), EMVI(−), EMR(−)	Bad	2	(−)	−	ulcer	İc (TP)	FN	TN	FN	TP	TN	TP	TP	N	ypT2N0M-	40%	TME
T3c, N(+), CRM(+), EMVI(+), EMR(+)	Ugly	3	(+)	(+)	ulcer	İc (TP)	TP	FP	TP	TP	TN	TP	TP	N	ypT3N0M-	50%	TME
T3d, N(+), CRM(+), EMVI(+), EMR(−)	Ugly	2	Insufficent	−	ulcer	İc (FP)	TN	TN	TN	TN	TN	TN	FP	N	ypT0N0	0	TME
T4a, N(+), CRM(−), EMVI(+), EMR(+)	Ugly	3	(−)	−	ulcer	İc (TP)	TP	TN	TP	TP	TN	TP	TP	N	ypT3N0M-	20%	TME
T4, N(+), CRM(+), EMVI(+), EMR(−)	Ugly	2	(−)	(+)	white skar	C (FN)	FN	TP	TP	TP	TP	TP	TP	N	ypT3N1aM-	1%	TME
T4, N(+), CRM(+), EMVI(+), EMR(−)	Ugly	2	(−)	(+)	white scar	C (FN)	FN	TP	TP	TP	TP	TP	TP	N	ypT2N1aM-	<%1	TME
T4, N(+), CRM(+), EMVI(−), EMR(−)	Ugly	3	(+)	−	White scar	C (FN)	TP	TN	TP	TP	TN	TP	TP	N	ypT3N0	3%	TME
T4, N(+), CRM(+), EMVI(+), EMR(−)	Ugly	3	(−)	(+)	White scar	C (TP)	TP	TP	TP	TP	TP	TP	TP	N	ypT3N1aM-	4%	TME
T3a, N(+), CRM(−), EMVI(−), EMR(−)	Good	2	(+)	−	ulcer	Ic (TP)	TP	?	TP	TP	?	TP	TP	N	ypT2	30%	LE
T3a, N(+), CRM(−), EMVI(+), EMR(−)	Bad	3	(−)	−	ulcer	Ic (FP)	FP	?	FP	TN	?	TN	FP	Y	ypT0	0	LE
T3b, N(−), CRM(−), EMVI(−), EMR(−)	Intermediate	3	(−)	−	white scar	C (FN)	TP	?	TP	TP	?	TP	TP	N	ypT2	<%1	LE
T3d, N(−), CRM(+), EMVI(−), EMR(−)	Ugly	3	(−)	−	white scar	C (TN)	FP	?	FP	TN	?	TN	FP	Y	ypT0	0	LE
T4, N(+), CRM(+), EMVI(−), EMR(−)	Ugly	3	(+)	−	ulcer	İc (TP)	TP	?	TP	TP	?	TP	TP	N	ypT2	60%	LE
T4, N(+), CRM(+), EMVI(+), EMR(−)	Ugly	3	(−)	−	ulcer	İc (FP)	FP	?	FP	FP	?	FP	FP	N	YpT0	0	LE

Table 4
MRI, magnetic resonance imaging; PET, positron emission tomography; CT, computed tomography; LN, lymph node; NPV, negative predictive value; PPV, positive predictive value.

	Endoscopy	MRI wall	MRI LN	PET CT wall
NPV	50%	50%	87.5%	100%
PPV	76.9%	76.9%	71,4%	93.3%
Sensitivity	71.4%	71,4%	83.3%	100%
Specivity	57,1%	57.1%	77,7%	85,7%
Accuracy	66,6%	66,6%	80%	95,2%

LARC patients. FDG-PET/CT, which originally evaluated the tumor metabolic activity using the glucose metabolism independent of morphological change, is useful for assessing the tumor response to treatment [28,29]. In fact, there is increasing data about PET/CT imaging using volume and metabolic estimates with individual standard uptake value thresholds for volume determination may provide a useful tool to predict response to nCRT in distal rectal cancer. Also, that response evaluation of FDG-PET/CT was significantly correlated to pCR of rectal cancer after CRT [30]. A pooled data show qualitative analysis after RCT is able to assess pCR with a negative predictive value of 89% and an overall accuracy of 65%, which is comparable to the quantitative SUV measurements post-RCT [31]. There is also growing data on the other methods to evaluate changes in MTV and TLG as a response parameter, such as Sun et al. found a relative decrease in MTV and TLG after 5–7 weeks significantly predictive for pCR [32].

In our system, cCR rates were evaluated by comparing the simultaneous PET/CT, MRI, and flexible endoscopy video recordings. The unanimity was mandatory. For example, inadequate TRG response, lack of a white scar, and/or FDG uptake continuity were evaluated as if there was no cCR on in the final stage.

On performing an endoscopic examination of the tumor in the intraluminal area (white-scar-formation), we observed that in 53.84% of the cases, it developed after 12 weeks. General approach, the duration required for the achievement of the maximum efficacy of generalized CRT was about 15–16 weeks, and the interval longer than 16 weeks might be causes a detrimental effect on surgical results. However, Garcia-Aguilar et al. clearly showed that despite the provision of more extensive chemotherapy before surgery, the postoperative complication rates did not differ based on the treatment arm. With a waiting period of 20 weeks in the SG4 group, the pathological complete response was found to increase (from 18% to 38%) [25]. In our patient group, consolidation chemotherapy application was useful in prolonging the waiting time as well as in the treatment of the primary tumor and LN metastasis. We noted that 66.6% of those in the LE group and 40% of those in the TME group who underwent surgery with no cCR decision had a live cell proportion lower than 1% in the final pathology report. Additionally, only 40% of those in the TME group, all of whom showed initial clinical LN-positivity, showed LN-positivity in the final pathology report.

Endoscopic luminal evaluation alone is not reliable. In the LE and TME groups, the sensitivity of endoscopy was 71.4%, specificity was 57.1%, PPV was 76.9%, and NPV was 50%. The ACOSOG Z6041 trial defined cCR as the complete disappearance of a tumor on proctoscopic examination and reported that an endoscopic sensitivity of 85% and specificity of 67% were predictors of complete pathological response. The associated false positive rate was 33% [33].

The most critical concern associated with the watch-and-wait protocol is local-regrowth and DM. Worldwide, the regrowth rates vary between 5 and 60% [17,34–39]. The main reasons for this difference are variations in the regrowth definition, follow-up protocols, and follow-up duration. In our study, the median follow-up period was 22 months, and local regrowth rate was 15.3%. Since we conducted a strict follow-up program, all the regrowth cases could be detected in the early stages and treated successfully with salvage surgery. In the literature, similar results have been reported in up to 95% of cases of salvage surgery in such groups of patients [35–37,40–44].

In our study, the development of DM among patients with cCR was one of the main concerns. In a meta-analysis, the results pertaining to the rates of cCR and pCR (6.8% and 8.7%, respectively) were similar among those with the watch-and-wait protocol after standard TME [45–47]. In this study, the rates of DM development were 5.1% in the NOM group, 12.5% in the TME group and 16.6% in the LE group. In the literature, the development rate of stage 2 systemic metastasis in ypTNM is greater than 35% [43].

As the cCR follow-up process requires the expertise of a dedicated multidisciplinary team, it may be difficult to apply in daily practice.

Limitations of the study

This study is limited by its short follow-up duration and small sample size, and its non-prospective design.

Conclusion

The concept of a cCR, to facilitate NOM bring about a paradigm shift in the management of selected patients with rectal cancer, in the era of effective different modality multimodality treatment. We have evaluated the effectiveness of the "Watch and Wait" strategy is based on the diagnosis of a cCR. The time to response assessment in studies is highly variable, ranging between 3 and 24 weeks. In our study, the time interval of 12 weeks (18 weeks from initiation of radiotherapy) after chemoradiotherapy was evaluated as most adequate to evaluate endoscopically cCR rate. Also, the multimodality imaging combining with PET/CT which have shown promising results with the significantly high NPV, in the evaluation of cCR. The cCR rates in our study were higher than those noted in previously published reports. Possible explanations for these current results were the use of TNT after CRT and prolongation of the time interval between completion of CRT and cCR. Besides with the slightly more intensive surveillance program possibly enabled detecting regrowths at an earlier stage, and thus positively affecting salvage and survival rates surgery, seven (46.6%) cases, the proportion of live tumor cells was lower than 1%. In the LE group, four (66.6%) of the six patients had a live cell proportion lower than 1%. Six patients (28.57%) from the surgery group, three (60%) in the LE group, and three (20%) in the TME group achieved cPR.

Our results indicated that a high proportion of selected rectal cancers could potentially be managed nonoperatively, and major surgery may be avoided.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.07.012.

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