"Watch and wait" approach in rectal cancer patients following complete clinical response to neoadjuvant chemoradiotherapy does not compromise oncologic outcomes

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ABSTRACT

Background/Aims: Although standart treatment for non-metastatic locally advanced rectal cancer includes neoadjuvant chemoradiation followed by surgical resection, patients who have achieved complete clinical response can be followed up without surgery.

Materials and Methods: Between 2010 and 2016, 61 patients received neoadjuvant chemoradiotherapy for low rectal cancer. Those patients who achieved clinical complete response were included in the "watch and wait" protocol and did not receive surgery. The remaining patients underwent radical surgery and some of these were diagnosed as having complete response pathologically. This study compared the oncological results of clinically complete responders with those patients defined as pathologically tumor-free.

Results: Seven patients who received neoadjuvant chemoradiotherapy were re-staged as having complete clinical response and included in the "watch and wait" approach protocol. The 5-year disease free survival was 100%. Mean follow-up was 63 months and the mean age was 57.3. Fifty-four patients underwent radical surgery and 7 of them were diagnosed as having pathological complete response. The 5-year survival was 100%. Mean follow-up was 56 months and the mean age was 50.6. All patients except one are alive without tumor recurrence in the surgery group. However, those who received surgery experienced significant morbidities due to their surgery.

Conclusion: The oncological results of the "watch and wait" approach patients were no different from the patients who received radical surgery and were diagnosed as having pathological complete response. Those patients in particular who required abdomino-perineal resection before chemoradiation should be informed about this approach if they have achieved complete response clinically.

Keywords: Rectal cancer, watch and wait, neoadjuvant chemoradiotherapy, clinical complete response, pathological complete response

INTRODUCTION

Rectal cancer affects nearly 6,000 new patients each year in Turkey according to the Turkish Ministry of Health (1). The management of rectal cancer has evolved considerably over the last few decades, with an increasing use of neoadjuvant chemoradiotherapy (nCRT). Currently, nCRT followed by a total mesorectal excision for patients with non-metastatic locally advanced rectal cancer is the mainstay of clinical management. It has a number of potential advantages, including a complete clinical or pathological response in 10%-30% of patients (2-4). A clinical response is defined as no signs of tumor on digital rectal examination, at endoscopy, and on imaging techniques. Patients with no clinical response can be suitable candidates for non-surgical management and follow-up without surgery. Those patients who particularily required abdomino-perineal resection before chemoradiation choose the "watch-and-wait" approach when given necessary information. A pathologically complete response is defined as an absence of tumor on a histological examination of the specimen following surgery. This raises the concern that some of patients may be over-treated surgically, leading to unnecessary ensuing morbidites. The present study compares the long-term outcomes of patients who selected the watch-and-wait approach with rectal cancer who progressed to a complete response clinically following nCRT compared to patients who received both nCRT and radical surgery and had a pathologically complete response or were tumor-free.

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MATERIALS AND METHODS

Between 2010 and 2016, a total of 61 patients with cT3/4N0M0 or cTanyN+M0 rectal cancer located within 10 cm of the anal verge (palpable with finger) underwent nCRT. Radiotherapy consisted of a total of 5040 cGy delivered in 28 fractions of 180 cGy, 5 times a week. During the 1st and 5th weeks of radiotherapy, 5-fluorouracil was given at a dose of 1000 mg per square meter. Patients were re-evaluated 8 weeks after the completion of nCRT using digital rectal examination, endoscopy, endosonography, MRI, and PET-CT studies, including biopsy of the tumor site. Patients were re-staged as complete clinical response (cCR) if tumor and lymph nodes could not be detected (Figure 1). They were all included in the watch-and-wait protocol and followed up every 3 months for a period of 2 years and 6 months subsequently. Three of these patients completed consolidation chemotherapy during that time. Other patients who were re-staged as an incomplete clinical response or no response to nCRT underwent radical surgery by the senior gastrointestinal surgeon. Suspicion of tumor on digital rectal examination, ulceration of the tumor bed, and PET/CT signaling were considered to have an incomplete clinical response. Patients with an incomplete clinical response initially and then diagnosed as tumor-free pathologically after surgery were considered as having a pathologically complete response (pCR) in the study (Figure 2). All pCR patients were followed up according to the NCCN guidelines, and none of them received adjuvant chemotherapy. Patients provided written consent for inclusion in the study. Ethics commitee approval has not been assigned for the study.

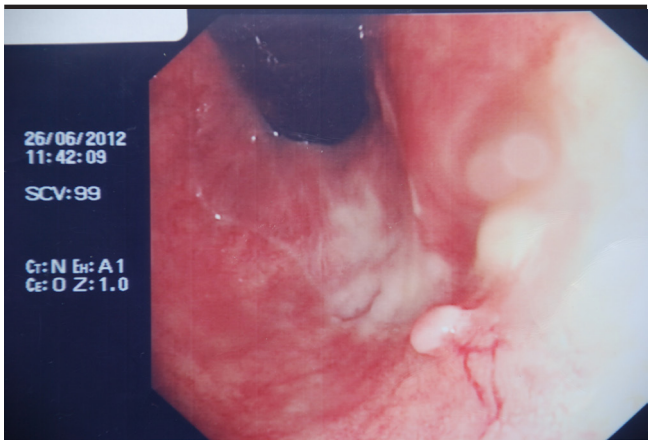

Figure 1. *Endoscopic apperance of the complete clinical response after neoadjuvant chemoradiotherapy.*

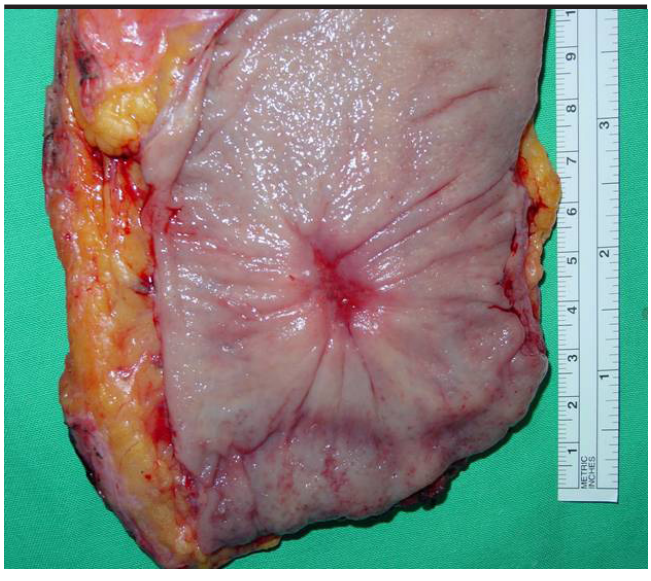

Figure 2. *Ulcer at the tumor site of a patient after neoadjuvant chemoradiotherapy diagnosed as incomplete clinical response initially and then diagnosed as pathological complete response after surgery.*

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences program version 22.0 (IBM Corp.; Armonk, NY, USA), and scale variables were expressed as the mean±standard deviation (median; min and max). Univariate analysis was performed using the chi-suared test, and Fisher's exact test in cross tables for compare the categoric variables between surgical and non-surgical groups or between gender. The Mann-Whitney U test was used for comparing the age, and the Kaplan-Meier log rank test was used to compare the survival between surgical and non-surgical groups. A p-value <0.05 was considered to be statistically significant in each test.

RESULTS

Seven patients (11.4%) who received nCRT were re-staged as having a cCR and included in the watch-and-wait approach protocol. The 5-year disease-free survival was 100%. The mean follow-up was 63 months (range, 34-104), and the mean age was 57.3 (range, 31-78). Patient and tumor characteristics are summarized in Table 1. All patients were alive with no evidence of tumor recurrence or distant metastasis. Fifty-four patients underwent total meso-rectal excision of whom 7 patients were re-staged as having had a clinically incomplete response, diagnosed as having a pCR or being tumor-free. Both the cCR and pCR rates were 22.8%. Patient and tumor characteristics are summarized in Table 2. The 5-year disease-free survival was 100% (Figure 3). The mean follow-up was 56 months (range, 28-94), and the mean age

Table 1. Patient and tumor characteristics of the "watch and wait" protocol patients

Patient	Age	Gender	Diagnosis Date	Tumor Stage	Control Biopsy
SY	1975	F	18.01.2010	cT2N+M0	YES
BK	1955	F	24.06.2011	cT3N0M0	YES
MA	1963	F	01.03.2012	cT3N0M0	NO
GA	1936	F	18.05.2015	cT3N+M0	NO
AK	1945	M	13.10.2015	cT3N0M0	NO
MH	1950	M	05.02.2016	cT3N+M0	NO
RB	1960	F	01.02.2015	cT3N0M0	NO

Control biopsy: biopsy of the tumor site after neoadjuvant chemoradiotherapy.

Table 2. Patient and tumor characteristics of the pathological complete responders

Patient	Age	Gender	Operation Date	Tumor Stage	Operation Type
BG	1974	F	24.09.2010	cT3N+M0	LAR
AK	1969	M	22.12.2010	cT2N+M0	LAR + Lİ
AT	1954	M	08.05.2013	cT3N+M0	LAR + Lİ
HT	1961	F	13.09.2013	cT3N0M0	APR
HK	1955	M	20.04.2015	cT3N+M0	APR
TK	1960	M	09.02.2016	cT3N0M0	LAR + Lİ
RS	1962	M	10.03.2016	cT4N+M0	APR

LAR: Low anterior resection; APR: Abdominoperineal resection; Lİ: Diverting loop ileostomy.

was 50.6 (range, 36-59). One patient died of an unrelated cause. There were no statistically significant differences between these two groups of patients in terms of age, gender, or tumor stage (Table 3). None of the patients experienced serious problems under the watch-and-wait protocol except for slight peri-anal complications such as excoriation, itching, and sensation of burning due to

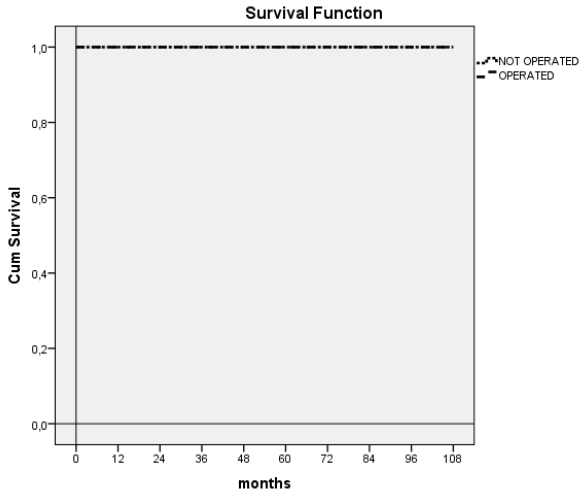

Figure 3. *Survival of patients according to operated and non-operated groups.*
There is no statistically significant difference between the groups since 5-year survival is 100.0% in both (p:1.000>0.05 According to Kaplan- Meier log rank test).

Table 3. Patient characteristics according to groups and subgroups

Characteristics		Surgery	Non-Surgery	Total	p (Surg vs Non-Surg)
		N%	N%	N%	
Gender	Male	5 71.4	2 28.6	7 50.0	0.286
	Female	2 28.6	5 71.4	7 50.0	
Age years	Male Mean + Std. D Median; Range	53.2+7.2 55; 41-59	67.0+2.8 67; 65-69	57.1+9.0 58; 41-69	0.095
	FemaleMean + Std. D Median; Range	44.0+11.3 44; 36-52	53.4+16.8 53; 31-78	50.7+15.2 52; 31-78	0.571
	Total Mean + Std. D Median; Range	50.6+8.7 53; 36-59	57.3+15.3 56; 31-78	53.9+12.5 54; 31-78	0.383
	p (between M vs. F)	0.190	0.381	0.180	-
T Stage	T2	1 14.3	1 14.3	2 14.3	0.580
	T3	5 71.4	6 85.7	11 78.6	
	T4	1 14.3	0 0.0	1 7.1	
N Stage	Negative	3 42.9	2 28.6	5 .7	1.000
	Positive	4 57.1	5 71.4	9 64.3	

radiotherapy. Those patients who underwent radical surgery and were diagnosed as being tumor-free experienced significant morbidities (57%), including two anterior resection syndromes, one rectovaginal fistula, and one peri-anal wound dehiscence.

DISCUSSION

nCRT for non-metastatic locally advanced rectal cancer is the standard of care because it is associated with a lower risk of local recurrence and improved functional results compared to adjuvant radiotherapy (5). The German Rectal Cancer Trial demonstrated that patients with cT3-4 tumors with a positive nodal status benefited from a 4% local recurrence rate at 5 years when undergoing preoperative CRT compared to a 13% local recurrence rate undergoing post-operative CRT (6). Furthermore, patients with tumors located in the lower third of the rectum treated with nCRT were twice as likely to undergo a sphincter-saving operation due to tumor downstaging (7). Despite excellent oncologic outcomes with nCRT followed by radical surgery, multiple studies have shown an absence of viable malignant cells in surgical resection specimens defined as pCR in 15%-40% of cases (8,9). Upon questioning the utility of surgery for pCR patients, the watch-and-wait protocol without surgery has been developed by Habr-Gama et al. (10). This Brazilian study has demonstrated 97% 5-year survival for watch-and-wait patients comparable to pCR patients treated with invasive surgery (11,12). In our experience, 7 patients were included in a watch-and-wait protocol without surgery, and we have previously published our findings for the first three patients (13). Currently, all of our patients achieved 100% 5-year disease-free survival, and to the best of our knowledge, this figure is the highest in the literature.

As nCRT may lead to a cCR, the clinical assessment of post-CRT staging is of upmost importance. The definition of a cCR by Habr-Gama et al. is whitening of the mucosa and telengiectasia with mucosal integrity (14). There should be no ulceration, residual nodules, or stenosis at the tumor site. Biopsy or trans-anal local excision can accurately assess the tumor response after chemoradiotherapy. We performed 1 trans-anal excision and 1 biopsy of the tumor site for the first 2 patients. There were no signs of tumor in either case. Other patients refused the biopsy or surgery. All of our patients decided to forego surgery since they would have required an abdomino-perineal resection before nCRT.

An endorectal ultrasound can accurately define the depth of tumor invasion with high sensitivity and specificity rates of 90% and 85%, respectively (15). However, restaging after neoadjuvant therapy is a challenge because of radiation-induced fibrosis, edema, inflammation, and necrosis. The sensitivity and specificity rates drop to 40% and 75%, respectively (16). Furthermore, there is some inaccuracy in determining the circumferential margin.

MRI is the gold standard for the local staging of rectal cancer before chemoradiotherapy, but the role of MRI in the selection of cCR patients is questionable (17). A pooled analysis of 33 studies that reported on restaging with MRIs revealed that the overall sensitivity and specificity was 50% and 91%, respectively (18). Conventional MRIs cannot differentiate between fibrosis and a tumor. A new functional magnetic resonance technology has the potential to improve the identification of a cCR.
The lymph node status after chemoradiotherapy was found to be an independent predictor of survival (19). Neither of the modalities mentioned here can accurately detect malign lymph nodes without surgery. PET is valuable for predicting the response of rectal carcinoma to neoadjuvant therapy. A meta-analysis reported 78% sensitivity and 66% specificity for the prediction of response (20).

In summary, there is no reliable test to predict pCR following nCRT for rectal cancer. No randomized controlled trials exist, comparing the watch-and-wait protocol with a standard nCRT followed by surgery. Given these reasons, surgeons and patients tend to choose radical surgery for safety and legal issues. However, many studies including a systematic review and pooled analysis have changed the management of a subset group of patients with rectal cancer in favor of the watch-and-wait strategy in recent years (21). No survival benefits from the surgery over the observation group have been revealed so far, to the best of our knowledge (22,23). Moreover, surgical complications have been associated with adverse oncological outcomes (24).

The watch-and-wait approach may initially cause distress to the patients as it may seem to be a risky approach to a serious disease. However, it does not mean that nothing is done; the patients are seen regularly and are very closely monitored for signs of disease recurrence. The studies indicate that recurrence during the observation period may occur within 12 to 18 months and that local recurrence can be salvaged with surgery (25,26). Surgery can safely be deferred until the tumor reappears. In the meantime, consolidation chemotherapy is an option that can increase disease-free survival. Radiation dose escalation and con-

solidation chemotherapy may have the potential to increase the organ preservation rates and improve survival in patients with locally advanced rectal cancer (27,28).

Our study is limited due to its small number of patients and the single-institution approach. Despite these limitations, and to the best of our knowledge, we believe that this is the first study in Turkey to clearly document the watch-and-wait protocol results comparing pathologically tumor-free patients. The findings of this study demonstrated that some of the patients with rectal cancer can be treated with chemoradiotherapy alone, such as those with anal squamous cell cancer.

To date, our oncological results from patients subjected to the watch-and-wait approach are no different from the patients who underwent radical surgery and were diagnosed as tumor-free. Those patients who need abdomino-perineal resection before chemoradiation should be consulted over this approach if they showed a cCR.

Ethics Committee Approval: *N/A.*

Informed Consent: *Written informed consent was obtained from all patients who participated in this study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - G.N.; Design - G.N.; Supervision - G.N., A.E.D.; Resources - G.N., A.E.D.; Materials - G.N., A.E.D., H.C.M., S.S.; Data Collection and/or Processing - G.N., A.E.D., S.S.; Analysis and/or Interpretation - G.N., A.E.D., H.C.M., S.S.; Literature Search - G.N., A.E.D., H.C.M., S.S.; Writing Manuscript - G.N., A.E.D.; Critical Review - A.E.D., H.C.M., S.S.*

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