

Oncologic Outcome to Neoadjuvant Chemoradiation for Rectal Carcinoma after Surgery (NCI -Cairo and Minia Oncology Center Experience)

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Abstract: Background: Surgery is the mainstay of curative treatment for carcinoma of the rectum. Neoadjuvant chemoradiotherapy (CRT) and an 8week hiatus may give a chance to spare a major surgical procedure in a subset of patients with rectal carcinoma. The current retrospective study studied the correlation between the clinical response assessment after neoadjuvant therapy and tumor regression grade in post-operative pathological examination. We tried to identify the category of patients who may benefit from “watch and wait” protocol to avoid the morbidity of surgical intervention. **Patients and Methods:** The current retrospective study included 124 patients with histologically proven stage II-III rectal adenocarcinoma treated at NCI-Cairo and Minia Oncology Center during the period between January 2010 and December 2015. All patients were to be treated by neoadjuvant CRT followed by surgical intervention. Post-operative pathological response was compared with the clinicopathologic characteristics as well as the pre-operative clinical response after neoadjuvant CRT. **Results:** Among the study group, 120 patients were subjected to surgery. In 30 patients (25%) there was no viable tumor cells in the surgical specimen (Group 3). Pathological examination documented mild response (Group 2) in 56 patients (46.7%) and no response (Group 1) in 34 patients (28.3%). There was no statistically significant difference as regards the clinicopathologic characteristics of patients according to the degree of pathologic response to neo -adjuvant therapy. The correlation between the clinical response after neoadjuvant therapy and the pathologic response after surgical intervention was studied. It was found that out of the 6 patients who showed complete clinical remission, no viable tumor cells were documented in only one patient (17%). Moreover, out of the 54 patients who showed partial clinical remission, no viable tumor cells were documented in 24 patients (44%). Among the 48 patients who showed clinically stable disease, no viable tumor cells were documented in 5 patients (11%). Thus, the majority (80%) of patients with no viable tumor cells had partial clinical response while only 3.3% had clinical complete remission and 16.7% had clinically stable disease after neo adjuvant therapy. As regards the overall survival rates, there was no significant difference in survival according to the clinical response after neoadjuvant therapy. On the other hand, the degree of pathologic response significantly affected the survival (p-value 0.002). **Conclusions:** The extent of clinical response after neoadjuvant therapy is not always a true indicator for the pathologic response after surgical intervention. The “watch and wait” approach may be a valid option not only for patients achieving complete clinical remission but also for some patients, who show partial or even stable disease after neoadjuvant therapy if properly evaluated. [Amani Saber, Ahmed Abdel -Latif, Hisham El-Hossieny, Hani Habashy. **Oncologic Outcome to Neoadjuvant Chemoradiation for Rectal Carcinoma after Surgery (NCI -Cairo and Minia Oncology Center Experience).** *Cancer Biology* 2018;8(2):34-41]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). <http://www.cancerbio.net>. doi: [10.7537/marscbj080218.04](https://doi.org/10.7537/marscbj080218.04).

Keywords: Rectal cancer, pre-operative concurrent chemoradiotherapy, surgical outcome.

1. Introduction

Colorectal cancer is a major worldwide health problem. It is the third most common cancer and the third leading cause of cancer death in men and women in the United States¹. In Egypt, colorectal cancer constitutes 4.2% and comes at seventh rank (7th in men and 4th in female)².

Surgery is the mainstay of treatment for colorectal cancer. However, radiotherapy and chemotherapy, if applied before surgery, may alter the pathologic T and N categories. This is achieved by reducing the depth of tumor invasion and, in a varying

percentage, by causing even complete disappearance of the malignant cells in the rectal wall and in perirectal lymph nodes^{3,4}. Habr-Gama and associates⁵ have shown that in the setting of complete tumor regression after neoadjuvant CRT and an 8 week hiatus, patients with no residual disease may have a chance to avoid the current major standard abdominoperineal resection⁵. The morbidity that comes with such an operation as temporary/permanent stoma, sexual dysfunction, and fecal incontinence can be avoided by this “watch and wait” protocol. While patients with residual disease may have surgery

postponed or delayed without oncological compromise⁶.

However, complete tumor regression after neoadjuvant CRT should be defined accurately and assessed meticulously. Maas et al⁷ defined the clinical complete response (cCR) as a considerable downsizing with no residual tumor or residual fibrosis only (with low signal on high b-value DWI, if available); no suspicious lymph nodes on MRI; no residual tumor at endoscopy or only a small residual erythematous ulcer or scar; negative biopsies from the scar, ulcer, or former tumor location; and no palpable tumor, when initially palpable with digital rectal examination. Residual wall thickening due to edema only is also an indication for a possible cCR. If patients did not meet all of these criteria, they were regarded as noncomplete responders⁷.

Therefore, identifying the 15%-20% of patients who achieve a complete response to neoadjuvant therapy is a real challenge. Digital rectal examination (DRE), endoscopy, endo-rectal ultrasosnography (ERUS), CT, MRI and positron emission tomography (PET) are considered the tools to determine tumor response. However, none of these modalities are capable of accurately predicting pathological complete response (pCR). Radiation induced fibrosis and inflammation limit their accuracy⁷. The overall concordance between DRE and pathologic response following neoadjuvant chemoradiotherapy is only 22%⁸. In addition, Marettoet al⁹ showed that only half of patients who were defined as having complete response on endoscopic biopsy had true pCR according to pathological evaluation of the surgical resection⁹.

Because of the limited accuracy of all existing imaging modalities in staging rectal cancer post-neoadjuvant chemoradiation, several groups have investigated other imaging methods as Diffusion-weighted MRI^{10,11,12}. However, the role of this emerging method is still investigational, and more studies with larger numbers of patients are awaited.

In the current retrospective study, we tried to identify the category of our patients with rectal carcinoma who may benefit from "watch and wait" protocol and avoid the morbidity of surgical intervention. Post-operative pathological response was compared with the clinicopathologic characteristics as well as the pre-operative clinical response after neoadjuvant CRT.

2. Patients and Methods:

The current retrospective study included 124 patients with histologically proven rectal adenocarcinoma treated at NCI-Cairo and Minia Oncology Center during the period between Jan 2010 and December 2015. The study group included

patients with locally advanced disease. The eligible patients had been subjected to clinical and radiological (CT scan and whenever available MRI) examination in addition to endoscopic assessment for the extent and location of the lesion. Patients included in the current study had stage II and III according to the American Joint Committee on Cancer version 6¹³.

All patients included in the current study received neo-adjuvant CRT. Radiotherapy was delivered by a 6MV linear accelerator using three or four fields to a total of 45 Gy, at a daily fraction of 180 cGy for 5 days per week. Chemotherapy was in the form of either 5 fluorouracil 400 mg/m² during the first and last weeks of radiation course or daily oral capecitabine 825mg/m² twice daily during radiotherapy days.

Assessment of response to neo-adjuvant treatment was planned to be performed 6 weeks after the last day of radiotherapy. They were assessed by clinical examination including DRE, radiologic assessment including CT scan and MRI and endoscopic examination. Response to neo-adjuvant therapy was performed according to the response evaluation criteria of revised RECIST assessment guidelines in solid tumors¹⁴. Table (1).

Table (1): Revised RECIST guidelines¹⁴

Grade of response	Response Criteria
Complete Response CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease SD	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.
Progressive Disease PD	At least a 20% increase in the sum of diameters of target lesions, the appearance of one or more new lesions is also considered progression.

After clinical, radiological and endoscopic assessment, patients wereto be subjected to surgical intervention (Abdomino- perineal or low anterior resection). The pathologic response was graded into 3 groups. The assessment system applied in the current study was modified and based on the criteria of the grading scale established by Dworaket al¹⁵.

Table (2): The Tumor response grading (TRG) system

The grading of Dworak et al ¹⁵		The modified system applied in the current study	
Grade	Definition	Group	Definition
Grade 0	No regression	Group 1	No regression or regression <50%
Grade 1	Minimal response <25% (dominant tumor mass with obvious fibrosis, vasculopathy)		
Grade 2	Moderate response >25%-50% (dominant fibrotic changes with a few easy-to-find tumor cells or groups)		
Grade 3	Near complete response >50% (few microscopically difficult-to-find tumor cells in fibrotic tissue with or without mucous substance)	Group 2	> 50% regression
Grade 4	Complete regression (no tumor cells, only fibrotic mass or acellular mucin pools)	Group 3	Complete regression (no tumor cells)

We tried to identify the clinical factors that are associated with the achievement of complete pathologic response (Group 3) among our patients with advanced rectal carcinoma. The characteristics of patients who achieved complete pathologic response to neo-adjuvant therapy were compared to those who showed partial (Group 2) or no response (Group 1).

Patients with complete pathologic remission with no viable tumor cells were left for follow-up. While patients with partial or no pathologic response received 6 cycles of chemotherapy (FOLFOX protocol).

Statistical methods:

Comparisons between the two groups were tested using either Chi-square test or Fishers exact test for categorical data. For quantitative data comparison between 2 groups was done using either parametric or non-parametric t-test as appropriate.

The survival rates of our patients were calculated from the date of diagnosis to date of last follow up in their records. Survival analysis were done using Kaplan-Meier method and comparison between survival curves was done using Log rank test. A p-value less than 0.05 was considered statistically significant. All tests were two tailed.

3. Results

All patients included in the current study were subjected to surgical intervention after neo adjuvant therapy except 4 cases. These 4 patients showed complete clinical response after neo adjuvant therapy and they refused to be subjected to surgical intervention. They received adjuvant chemotherapy (FOLFOX) for 6 cycles and were kept under follow-up. All the 4 patients are in maintained remission for a period of 15,18,20 and 22 months from the date of end of radiotherapy.

The remaining 120 patients were subjected to surgical intervention. Surgery was planned to be performed 6 weeks after the end of radiotherapy.

However, because of some medical, social and /or administrative reasons, the intervention was performed after a range from 4 -16 weeks from end of radiotherapy (Table 3). Pathological examination of the surgical specimen showed no detected viable tumor cells in 30 patients (25% - 30/120) (pathologic complete remission, Group 3). Pathological examination documented mild response (Group 2) in 56 patients (46.7%- 56/120) and no response (Group 1) in 34 patients (28.3% - 34/120) Figure (1).

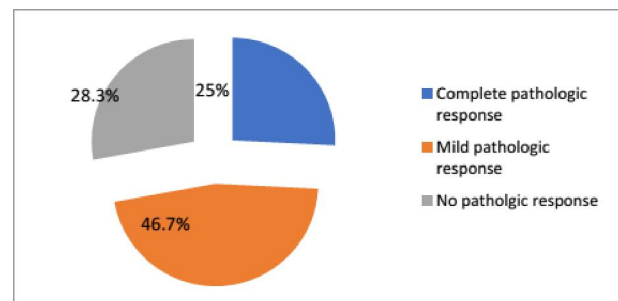


Figure (1): The pathologic response among our patients with advanced colorectal carcinoma treated by neo-adjuvant therapy followed by surgical intervention

To study the clinical factors that may be associated with the results of the pathologic response, the clinicopathologic characteristics of patients were compared according to the degree of pathologic response to neo -adjuvant therapy.

Table (3) there was no statistically significant difference.

The relation between the clinical response after neoadjuvant therapy and the pathologic response after surgical intervention among our patients was studied [Table (4) and Figure (2)]. It was found that out of the 6 patients who showed complete clinical remission, no viable tumor cells were documented in only 1 patient (17%). Moreover, out of the 54 patients who showed

partial clinical remission, no viable tumor cells were documented in 24 patients (44 %). Among the 48 patients who showed clinical stable disease remission, no viable tumor cells were documented in 5 patients (11%) Table (4). Thus, the majority (80%=24/30) of

patients with no viable tumor cells had partial clinical response while only 3.3 %(1/30) had clinical complete remission and 16.7%(5/30) had clinical stable disease after neo adjuvant therapy. Figure (2).

Table (3): The clinicopathologic characteristics of patients with advanced colorectal carcinoma treated by neo-adjuvant therapy followed by surgical resection according to the result of the pathologic response

TRG	Complete regression Group 3		Regression>50% Group 2		No 50%regression or< Group 1		Total	
	No.	%	No.	%	No.	%	No.	%
Age (years) <i>range</i> ≤ 40 > 40	24-69 15 15	 50 50	23-70 34 22	 60.7 39.3	19-70 18 16	 52.9 47.1	67 53	55.8 44.2
Sex <i>Male</i> <i>Female</i>	13 17	43.3 56.7	24 32	42.9 57.1	16 18	47.1 52.9	53 67	44.2 55.8
Pathology <i>Adenoca.</i> <i>Mucinous adenoca.</i>	26 4	86.7 13.3	42 14	75 25	29 5	85.3 14.7	97 23	80.8 19.2
Distance from anal verge <i>Median</i> ≤ 4 > 4	5 14 16	 46.7 53.3	5 24 32	 42.9 57.1	5 8 26	 23.5 76.5	46 74	38.3 61.7
Time from last day of Rt to surgical intervention in weeks <i>range</i> < 6 6 > 6	5-12 4 9 17	 13.3 30 56.7	3-12 10 10 36	 17.9 17.9 64	4-16 4 2 28	 11.8 5.9 82.3	18 17 65	15 17.5 67.5
Type of surgical intervention <i>APR</i> <i>LAR</i>	14 16	46.7 53.3	34 22	60.7 39.3	14 20	41.2 58.9	49 47	51.7 48.3
Total	30	25	56	46.7	34	28.3	120	100

Table (4): The relation between the clinical and pathologic response among patients with advanced colorectal carcinoma treated by neo-adjuvant therapy followed by surgical resection

Pathologic TRG Grade of Response to neoadjuvant therapy	Complete pathologic regression Group 3		Pathologic Regression ≥ 50% Group 2		No or < 50% pathologic regression Group 1		Total	
	No.	%	No.	%	No.	%	No.	%
Complete response	1	17	5	83	0	0	6	5
Partial response	24	44	15	28	15	28	54	45
Stable disease	5	11	29	60	14	29	48	40
Progressive disease	0	0	7	58	5	42	12	10
Total	30	25	56	46.7	34	28.3	120	100

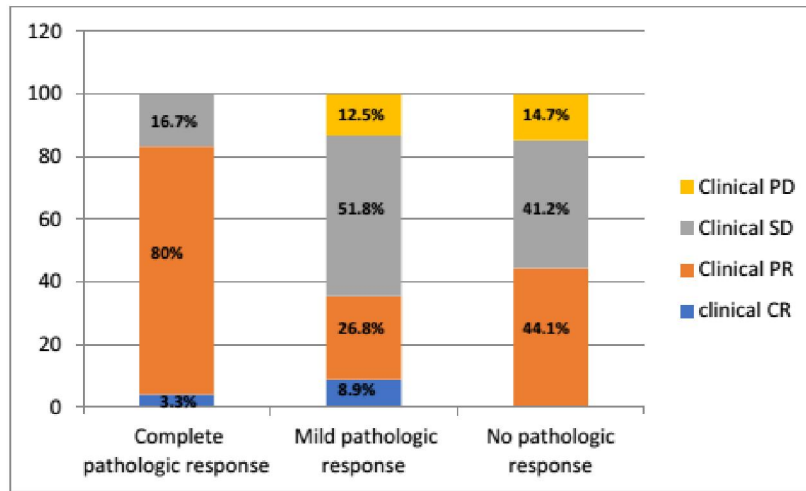


Figure (2): The relation between the clinical and pathologic response among patients with advanced colorectal carcinoma treated by neo-adjuvant therapy followed by surgical resection

As regards the overall survival rates, there was no significant difference in survival according the clinical response, however, the degree of pathologic

response affected the survival significantly. Figure (3A, B).

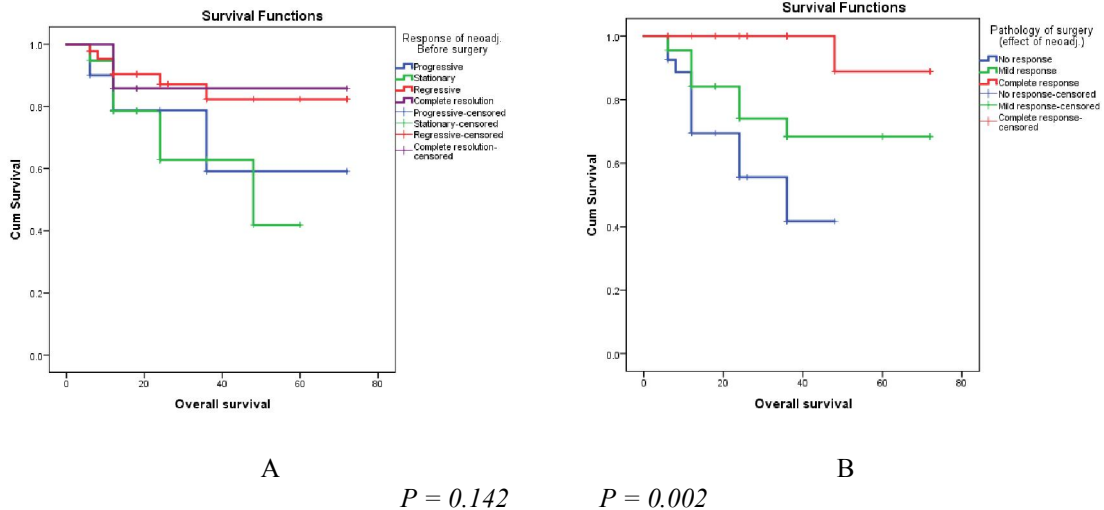


Figure (3): The survival rate in patients with advanced colorectal carcinoma treated by neo-adjuvant therapy followed by surgical resection in relation to the clinical response after neo adjuvant therapy (A) and according to the pathologic response after surgical intervention (B)

4. Discussion

Early in 1997, the Swedish Rectal Cancer Trial proved that preoperative radiotherapy followed by surgery had reduced local recurrence (11% versus 27%) and better survival than surgery alone (5-year overall survival of 58% versus 48%)¹⁶. This changed the concept of low rectal cancer management. In a more recent study, Habr-Gama and associates have shown that in the setting of complete tumor regression

after neoadjuvant CRT and an 8week hiatus, patients with no residual cancer may have a chance to be spared the current major standard abdominoperineal resection⁵.

Both clinical and radiological assessment are important for adequate staging and may aid in the distinction between pathological complete and incomplete response^{17,18,19}. Digital rectal examination (DRE), endoscopy, endo-rectal ultrasnography

(ERUS), CT, MRI and positron emission tomography (PET) are considered the tools to determine tumor response. However, none of these modalities are capable of accurately predicting pCR. Radiation induced fibrosis and inflammation limit their accuracy^{7,8}. In addition, Maritto et al⁹ showed that only half of patients who were defined as having complete response on endoscopic biopsy had true pCR according to pathological evaluation of the surgical specimen. Thus, identifying the 15%-20% of patients who achieve a complete response to neoadjuvant therapy is a real challenge.

In the current study, assessment of response to neo-adjuvant treatment was performed in the majority of patients after more than 6 weeks (range 4-16) from the last day of radiotherapy by clinical, radiologic (CT scan and MRI) and endoscopic examination. The majority of patients (80%) with no viable tumor cells in the surgical specimen (pathologic complete remission) showed partial clinical response to neo-adjuvant therapy while only 3.3% showed clinical complete remission. Moreover, in 11.7% of patients with pathologic complete remission assessment was graded as clinical stable disease after neo-adjuvant therapy. The current study confirms the discrepancy between the results of pathologic response and the clinical response after neo-adjuvant therapy. Same results were reported by Guillem et al⁸ and Maretto et al⁹. Because of the difficulty in predicting the pathologic complete remission, surgery still remains the standard of care for rectal cancer patients.

Factors that predict patients' response to neoadjuvant CRT for rectal cancer have not been well defined. Several small retrospective studies have showed some clinical factors and molecular biomarkers as predictors of tumor response to CRT, including the pre-treatment tumor size, site, carcinoembryonic antigen (CEA) level, epidermal growth factor receptor p21 and microsatellite instability^{20,21,22,23, 24}. Janian and his colleagues³ showed that small middle and lower tumors with low pre-treatment carcinoembryonic antigen level benefited more from the neoadjuvant CRT. However, the pre-treatment CEA level in a majority of patients is normal and the cut-off level is inconclusive. Therefore, the applicability of CEA in predicting treatment response remains unclear²⁵.

In a recent study, van der Sluis et al²⁶ found that the best response rate was observed in patients diagnosed with a non-obstructive, well and moderately differentiated adenocarcinoma of the lower rectum with no clinical apparent nodal or distant metastatic disease (pCR ratio 18.8%). The percentage of patients demonstrating pCR decreased in case of symptoms of pretreatment obstruction or poorly differentiated tumors (pCR ratio of 11.8 and 6.7%, respectively)²⁶.

Also, the interval from end of pre-operative treatment to surgery of more than 7 weeks was associated with an increased rate of pCR²³.

In the current retrospective study, the pre-treatment characteristics of patients according to the degree of pathologic response after surgical intervention were compared. There was no statistically significant differences regards age, sex, pathological subtype, distance from anal verge, and type of surgery. This may be explained by the limitation of information that can be collected from the medical files for retrospective studies.

It is of note that patients undergoing cCR have an improved disease free and overall survival than those who have a partial response²⁷. An interesting paper from Wynn et al²⁸ found more than seventy descriptions of complete response after neoadjuvant CRT within the United Kingdom alone calling for an international, if not, only a national classification of response. No one clear definition within current literature appears dominant over the other. This may explain partly the discordance between the treatment results in the different studies. In the study of Habr-Gama et al²⁹, the 5-year overall survival disease free survival rate of those patients who obtained clinical complete remission through preoperative chemoradiotherapy reached 83% and 92% respectively.

In the current study, the survival rates of patients who achieved complete or partial clinical response to neo-adjuvant CRT was better than those who had stable or progressive disease. However, these results do not show statistical significance. On the other hand, the grade of pathologic response significantly affected the survival rates. This shows that our system for the clinical assessment of remission after neo adjuvant therapy is not optimal and the identified clinical remission does not reflect the real disease status. We may need to review and develop our protocol of assessment of clinical remission in an attempt to improve its accuracy. However, there is still international confusion about the protocol of assessment of clinical response after neoadjuvant CRT and about the influence of clinical response grade on treatment success. Thus, physicians are still reluctant to treat patients without using surgery, mainly because of the lack of a sufficiently accurate technique for identifying patients with a cCR^{23,25}.

In conclusion, pre-operative concurrent chemoradiotherapy is widely accepted as an effective way to achieve local control and subsequently survival benefit in patients with locally advanced rectal cancer. The accuracy of preoperative staging is crucial in preventing under- or over-treatment. Prospective studies conducted on larger number of patients with special stress on symptoms of pretreatment obstruction

and tumor site, size and differentiation should be encouraged to reach firm conclusions about patients who may be good candidates for the “watch and wait” protocol. Unification of definition of clinical complete response with use of a sufficiently accurate technique for identification of these patients, optimal drug combination and /or targeted therapy should be our crucial goal. The challenges include individualizing care to improve long-term oncologic outcome, while minimizing toxicity and maintaining quality of life.

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