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Predictors of tumor response to neoadjuvant chemoradiation in locally advanced rectal cancer Egyptian patients

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ABSTRACT

Background: Neoadjuvant chemoradiotherapy (CRT) followed by surgery is the standard of care for locally advanced rectal cancer. Pathological complete response (pCR) has been associated with decreased local recurrence and improved survival. Means of predicting the pathological response remain incompletely defined.

Materials and Methods: A single-institution prospective analysis of 120 patients with LARC treated with standard neoadjuvant CRT followed by total mesorectal excision. Histological examination of the surgical specimen was performed to assess the pathological response, which was categorized as pCR, downstaging or non-responders. Variables were analyzed by uni- and multi-variate analyses to identify any factors that could predict tumor pathological response.

Results: Of total 120 studied patients, only 5% achieved pCR and 73.3% of patients had downstaging. In the multivariate analysis, tumor grade (P = 0.024) and the distance from the anal verge (AV) (P = 0.032) were the only independent predictors of response to neoadjuvant CRT. Using logistic regression analysis of different combinations of predictive variables revealed that the combination of tumor grade, the distance from AV and negative nodal status is the strongest model that could predict tumor response to neoadjuvant CRT with accuracy of 90.7%.

Conclusion: High-grade distal tumors without lymph node metastasis could obtain a better response to neoadjuvant CRT.

Key words: *Pathological response predictors, neoadjuvant chemoradiation, locally advanced rectal carcinoma*

Introduction

Colorectal cancer (CRC) is the fourth most frequently diagnosed malignancy in both sexes and the second most common cause of cancer death in the world [1]. Locally advanced rectal cancer (LARC) is defined as one with clinical or radiological evidence of a T3/4 or N1 tumor. Neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) has been established as the standard treatment for LARC and results in high rates of local control with decreased morbidity and mortality compared with surgery alone or with postoperative adjuvant chemoradiation [2,3]. There is a large variability in response of LARC to neoadjuvant CRT, as some patients may not respond at all and even have the disease, while others have surgical specimens without any viable tumor cells, a pathologic complete response (pCR). Approximately 40-60% of LARC patients treated with neoadjuvant CRT achieve some degree of pathologic downstaging and the reported incidence of pCR ranges from 10% to 30%. pCR has been associated with decreased local recurrence, improved disease-free survival, and increased sphincter-preservation rates [3-6]. Predicting tumor response may be beneficial in anticipating treatment

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outcomes, optimizing treatment decisions and planning of risk-adapted treatment strategies. In addition, patients who are unlikely to respond could be offered alternative approaches to therapy. Many factors may predict tumor response to CRT, but until now, there has been no way to propose a model that would predict clinically or pathology complete or partial tumor response after CRT [7-10].Our aim was to identify any clinical, pathological, and therapeutic factors that could predict tumor response (complete pathologic response [CPR] or downstaging) to neoadjuvant CRT in LARC.

Patients and Methods

After Ethical Committee approval and taking patients' consents, a prospective analysis of 120 consecutive patients with LARC treated at Alexandria Main University Hospital was done in the period between 2009 and 2013. All patients were above 18 years and had histologically confirmed rectal adenocarcinoma, clinically and/or radiologically categorized to be locally advanced within 10 cm from the anal verge (AV). Patients with multiple synchronous, patients with contraindications to CRT and patients that refused treatment or to go through study were excluded. After obtaining an informed consent signed by all the patients, thoracoabdominal and pelvic computed tomography scans were done to exclude distant disease. Pre-neoadjuvant CRT evaluation included digital rectal examination, rigid proctoscopy, flexible endoscopy, and magnetic resonance imaging (MRI) of pelvis to all patients to detect tumor size, shape, extent of infiltration, sphincter relation, distance from AV and presence of metastatic lymph nodes (LNs).

The patients then received preoperative CRT in the form of preoperative whole-pelvis radiotherapy: With a mean dose of 45 Gy/25 fractions (five sessions every week for 5 successive weeks, using 18-MV photons beams and a three-field technique (one posterior field and two lateral fields). Concomitant chemotherapy was administered on the 1st day of pelvic radiation with either Mayo Clinic protocol: (5-fluorouracil (FU) 400 mg/m2/day and calcium leucovorin 20 mg/m2/day, five sessions every week for 5 successive weeks) or capecitabine protocol (825 mg/m2 twice daily, 5 days every week for 5 successive weeks).

About 4 weeks after completion of preoperative CRT, all patients underwent an evaluation in order to determine tumor response. This evaluation included digital rectal examination, rigid proctoscopy, flexible endoscopy, and MRI. Carcino-embryonic antigen (CEA) levels were determined before and after CRT using the same technical processes. Local extent of disease and evaluation of T and N stages were determined before and after CRT, based on pelvic MRI. The 7th edition of the American Joint Committee on Cancer TNM system was used for staging [11]. The surgical treatment was a proctectomy with TME, with or without sphincter preservation about 6-8 weeks after the end of CRT.

Histological examination of the operative specimen was performed to assess tumor type, grade, stage, number of retrieved and invaded LNs, maximum circumferential and distal extend, and venous or perineural invasion. Tumor regression grading (TRG) was done according to Dworak et al. [12] as follows:

- Grade 0: No regression.
- Grade 1: Poor response; dominant tumor mass with fibrosis involving less than 50%.
- Grade 2: Good response; dominantly fibrotic changes (more than 50%) with obvious residual tumor cells or groups (easy to find).
- Grade 3: Near complete response; few tumor cells (difficult to find microscopically) in fibrotic tissue with or without mucous substance.
- Grade 4: Complete response; no tumor cells, only fibrotic mass (total regression).

For statistical analysis, grouping of the 5-point TRG was done to avoid small categories that may lead to weaker results. We used three groups: Complete response, TRG 4, good response including TRG 2 and 3; and non-responders including TRG 0 and 1.

The following parameters were evaluated as potential predictive factors of tumor response: Age, sex, pretreatment tumor size, fixation, distance from AV, circumferential extent of tumor, tumor pathological type, grade, and clinical T stage, clinical LN (N) classification, pretreatment CEA level, type of chemotherapy (5-FU vs. capecitabine), and time interval between CRT and surgery.

Statistical Analysis

Data were summarized by frequencies and percentages for categorical variables. For continuous variables, medians, and ranges were computed. To determine the association between response and covariates, univariate analysis was performed using the nonparametric Chi-square test or Wilcoxon rank sum test when appropriate. Predictors of good response to neoadjuvant CRT were assessed using uni- and multi-variate analyses and logistic regression test.

Results

Among 120 studied patients, there were 68 males and 52 females. The age ranged between 35 and 72 years, with a mean of 52.6. The clinical and pathological characteristics of patients are described in Table 1. All the patients had a tumor within 10 cm from AV. The tumors had involved more than 50% of the rectal circumference in 66.7% of the cases. During digital rectal examination, the tumor was fixed in 26.7%. Radiological assessment by MRI revealed that 64 patients (53.3%) had nodal metastasis and 12 patients (10%) had tumor spread outside the rectum without fixation to surrounding structures (T4a), while 32 patients (26.7%) had tumor spread outside the rectum with in-

Table 1. Clinical and radiological assessment the tumor.

Clinical and radiological assessment the tumor	Total (*n*=120)	
	Number	Percentage
Distance from the anal verge (AV)		
≤6	41	34.2
6-10	79	65.8
Circumference		
≤25%	11	9.2
25-50%	29	24.1
50-75%	36	30
100%	44	36.7
Size of tumor		
>5 cm	85	70.8
≤5 cm	35	29.2
Fixation		
Fixed	32	26.7
Not fixed	88	73.3
Pretreatment TNM staging		
T4bN2M0	12	10
T4bNIM0	18	15
T4aN2M0	4	3.3
T4aNIM0	6	5
T4aN0M0	4	3.3
T3N2M0	8	6.7
T3N1M0	16	13.3
T3N0M0	52	43.3
Pathological grade		
Poorly differentiated	52	43.3
Moderately differentiated	47	39.2
Well differentiated	21	17.5

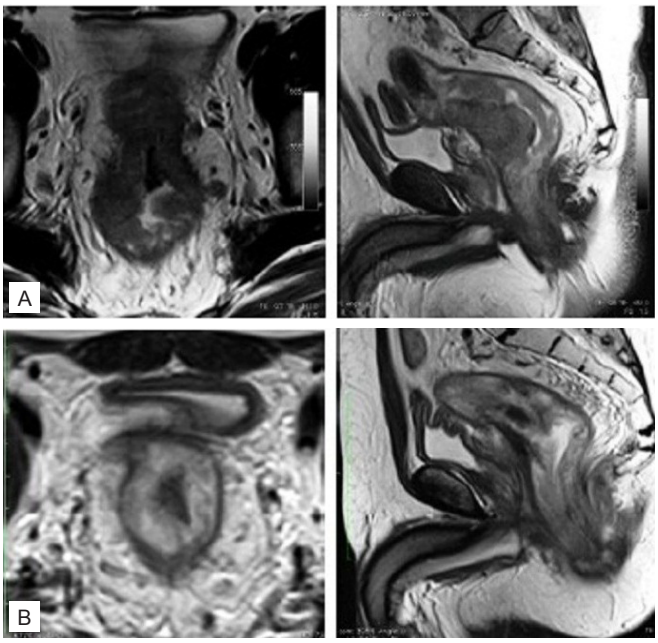

Figure 1. A: Magnetic resonance images of middle third locally advanced rectal cancer in a male patient before neoadjuvant chemoradiotherapy (CRT). **B:** Magnetic resonance images of the same patient after neoadjuvant CRT showing near complete response.

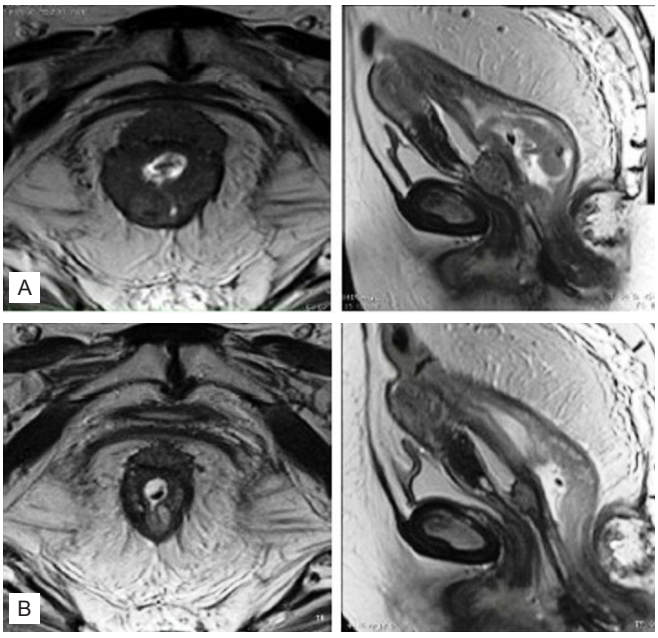

Figure 2. A: Magnetic resonance images of middle third locally advanced rectal cancer in a female patient before neoadjuvant chemoradiotherapy (CRT). **B:** Magnetic resonance images of the same patient after neoadjuvant CRT showing partial response.

filtration into surrounding structures (T4b). Pre-treatment CEA level of the studied cases ranged between 2 and 6 ng/dl with a mean of 4.01 ± 1.43 ng/dl. On pathologic examination of preoperative endoscopic biopsies, all tumors were adenocarcinoma, 43.3% of which were poorly differentiated.

About 86.7% of the included patients received concomitant preoperative chemotherapy according to the Mayo Clinic protocol, while 13.3% received capecitabine protocol. After the end of neoadjuvant therapy, the response was assessed radiologically by pelvic MRI and the results were that 76.7% of patients had complete or partial response [Figures 1 and 2] while 23.3% had no response.

Surgical treatment was done 6-8 weeks after the end of neoadjuvant therapy; 24 patients (20%) underwent abdominoperineal excision of the rectum (APR), APR combined with total abdominal hysterectomy in 4 patients (3.33%), and 92 patients (76.7%) had low anterior resection (LAR) (12 of them with a covering ileostomy). All operations had followed standard method of TME. Postoperative wound infection was encountered in 16 patients (13.3%), anastomotic leak in 12 patients (10%), and anastomotic stricture in 3 patients (2.5%).

The excised specimen was examined pathologically to assess the final pathological T and N stages. When compared to pretreatment MRI radiological T stage, there was a downstaging of pathological T stage in 80 patients (66.7%) and complete disappearance of the primary tumor in 6 patients (5%) [Table 2].

The number of LNs harvested was <6 LNs in 16 patients (13.3%), 6-12 LNs in 28 patients (23.3%), 12-18 LNs in 16 patients (13.3%), and 18-24 LNs in 60 patients (50%). As regards LN infiltration, no LNs were infiltrated (N0) in 60 patients (50%), N1 in 45 patients (37.5%) and N2 in 15 patients (12.5%). Thus, the removed LNs were infiltrated in 50% of patients. Nodal response to neoadjuvant CRT was lower than that of the primary tumor with only 10.8% down staging of N stage [Table 3].

Pathological complete response (pCR), defined as the absence of any tumor cells at both the primary site and in regional LNs was detected only in 4 patients (3.3%), 2 of the 6 patients with pT0 had residual disease in the mesorectal LN. Partial pathological response with downstaging of either T or N stage was detected in 88 patients (73.33%). Twenty-eight patients (23.33%) showed no downstaging of either T or N stage and were classified as non-responders [Table 4].

On univariate analysis, an inversely proportionate significant correlation was found between the response to neoadjuvant CRT and the distance from AV, the

Table 2. Comparison between pre-treatment radiological T stage and post-treatment pathological T stage.

Pre	Post					Total
	T4	T3	T2	T1	T0	
T4	20	15	4	3	2	44
T3	0	14	44	14	4	76
Total	20	29	48	17	6	120

Table 3. Comparison between pre-treatment radiological N stage and post-treatment pathological nodal stage (N stage).

Pre	Post			Total
	N2	N1	N0	
N2	15	9	0	24
N1	0	36	4	40
N0	0	0	56	56
Total	15	45	60	120

Table 4. Comparison between pre-treatment radiological TN stage and post-treatment pathological stage (ypT ypN stage).

Pre	Post													Total, *n*=120
	T4N2	T4NI	T4N0	T3N2	T3N1	T3N0	T2N2	T2N1	T2N0	T1N1	T1N0	T0N1	T0N0	
T4N2	8	2	0	0	6	0	0	0	0	0	0	0	0	16
T4NI	0	8	2	0	8	0	0	4	0	2	0	0	0	24
T4N0	0	0	0	0	0	2	0	0	2	0	0	0	0	4
T3N2	0	0	0	6	0	0	1	1	0	0	0	0	0	8
T3N1	0	0	0	0	6	2	0	4	0	2	0	2	0	16
T3N0	0	0	0	0	0	0	0	0	36	0	12	0	4	52
Total, *n*=120	8	10	2	6	20	4	1	9	38	4	12	2	4	120

Table 5. Predictors of response to neoadjuvant CRT, univariate analysis.

Clinical and radiological assessment the tumor	Non-responder (*n*=28)	Downstaging (*n*=88)	CPR (*n*=4)	(Rs) Spearman coefficient	*P* value
Distance from AV					
≤6	2 (7.1)	35 (39.8)	4 (100)	−0.759*c	<0.001*
6-10	26 (92.9)	53 (60.2)	0 (0)		
Circumference					
≤25%	0 (0)	7 (8)	4 (100)	−0.562*	0.003*
25-50%	0 (0)	29 (33)	0 (0)		
50-75%	8 (28.6)	28 (31.8)	0 (0)		
100%	20 (71.4)	24 (27.2)	0 (0)		
Pretreatment nodal stage					
N0	0 (0)	52 (59.1)	4 (100)	−0.774*	0.001*
N1	4 (14.2)	36 (40.9)	0 (0)		
N2	24 (85.8)	0 (0)	0 (0)		
CEA level					
<3.7 ng/dl	0 (0)	68 (77.2)	4 (100)	−0.416*	0.022*
>3.7 ng/dl	28 (100)	20 (22.8)	0 (0)		
Tumor grade					
Poorly differentiated	2	46 (59.1)	4 (100)	−0.685*	0.029*
Moderately differentiated	5	42 (40.9)	0 (0)		
Well differentiated	21	0 (0)	0 (0)		

CRT: Chemoradiotherapy, CPR: Complete pathologic response, AV: Anal verge, CEA: Carcino-embryonic antigen.

Table 6. Predictors of pCR or down staging, multivariate analysis.

Predictors	*P* value
Distance from anal verge	0.032*
Circumferential extent	0.154
CEA level	0.106
Nodal stage	0.25
Tumor grade	0.024*

pCR: Pathological complete response, CEA: Carcinoembryonic antigen

shorter the distance, the better the response. Furthermore, there was an inversely proportionate significant correlation between the response to neoadjuvant CRT and both the pretreatment circumferential extent of the tumor and the nodal stage. High tumor grade was associated with a significant better response to neoadjuvant CRT. After tabulation of the CEA level results and application of the ROC curve, the cut off point for CEA level to correlate with response was 3.7. A CEA level lower than 3.7 ng/dI was associated with a better response [Table 5]. In the multivariate analysis, tumor grade (P = 0.024) and the distance from AV (P = 0.032) were the only independent predictors of response to neoadjuvant CRT [Table 6]. Logistic regression analysis of different combinations of predictive variables revealed that the combination of tumor grade, the distance from AV and negative nodal status is the strongest model that could predict tumor response to neoadjuvant CRT ($\chi 2$ 45.278, P = 0.001). The accuracy of this combination was 90.7%.

Discussion

The objective of our study was to identify clinical, pathological, and therapeutic predictive factors of tumor response (either complete response or downstaging) in order to determine the stratification of patients and the adapted risk treatment. Brown et al. [13] registered 21 patients (24%) out of 89 LARC patients achieved PCR. Moureau-Zabotto et al. [14] conducted a study on 168 patients and reported pCR in 19%. In a large study on 562 patients of LARC received neoadjuvant CRT, Das et al. [7], reported 20% pCR. The lesser incidence of PCR reported in the current study may be due to small sample size, or specific nature of the Egyptian race.

A major problem during the application of neoadjuvant CRT is the risk of LN metastases despite complete primary tumor regression. Even in pathological T0 after neoadjuvant CRT (ypT0), the risk of LN metastases or mesorectal deposits as reported in previous studies is as high as 12%; thus, the decision to not pursue surgery after complete tumor response is still debatable [6,15-17]. In the current study, 2 out of 6 patients (33.3%) with ypT0 had residual disease in the mesorectal LN.

On univariate analysis, an inversely proportionate significant correlation was found between the response to neoadjuvant CRT and both of circumferential extent of the tumor and its distance from AV, nodal stage, and CEA level. Other different clinical and pathological studied factors were not predictive of tumor response to neoadjuvant CRT including patient's age, sex and body mass index, tumor length, shape, fixity, type and grade, pretreatment radiological T and N stage, tumor, pretreatment CEA level, radiotherapy dose, and type of chemotherapy. Although the multivariate analysis had failed to demonstrate any factor as an independent predictor of good response, logistic regression analysis, revealed that the combination of high grade tumor, closer/closeness to AV and negative nodal status is the strongest model that could predict better tumor response to neoadjuvant CRT ($\chi 2$ 45.278, P = 0.001). The accuracy of this combination was 90.7%.

Moureau-Zabotto et al. [14] outlined essentially three predictive factors for tumor downstaging: Small tumor size, chemotherapy by capecitabine, and CEA level <5 ng/ml. Das et al. [7] reported that circumferential extent of the tumor and distance from the AV independently predicted tumor downstaging, while circumferential extent significantly predicted pCR on multivariate analysis. In the same study, the CEA level significantly predicted both pCR and tumor downstaging on univariate analysis, but not on multivariate analysis. On reviewing the literature, many studies reported that a good tumor response to CRT is associated with a low level of determined pretreatment CEA [8,18,19]. Janjan et al. treated 117 patients with preoperative neoadjuvant CRT and found that the pretreatment tumor size was the only factor that was predictive of a CPR [20]. Berger et al. found that a higher dose of radiotherapy was the most favorable predictive marker for tumor downstaging after preoperative radiotherapy [21].

Recent studies have explored the role of molecular markers and gene expression profiling in predicting pathologic response of LARC to neoadjuvant CRT. Some demonstrated that expression of the epidermal growth factor receptor predicts a decreased pathologic response to preoperative chemoradiation [22,23].

Overexpression of cyclooxygenase-2 has been associated with a poor response to preoperative chemoradiation [24]. P53 and P27 gene mutations are significantly associated with radioresistance [25,26]. However, we did not evaluate biologic markers in the current study as predictors of tumor response because they are not investigated routinely in Egyptian LARC patients. Clinical, radiological, and pathological predictive factors are easily measurable and more cost effective.

Conclusions

From the present study, we can conclude that high-grade distal tumors closer to AV without LN metastasis are associated with a better response to neoadjuvant CRT.

This paper helps to individualize the neoadjuvant chemoradiation (CRT) in patients with locally advanced rectal cancer (LARC) by identifying any clinical, pathological and therapeutic factors that could predict tumor response (CPR or downstaging) to neoadjuvant CRT.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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