Impact of neoadjuvant chemoradiation on pathologic response and survival of patients with rectal cancer

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Objectives
The aim of this study was to assess the impact of neoadjuvant chemoradiation on the pathologic response and survival of patients with rectal cancer.
Background
Colorectal cancer is one of the most common human malignancies; there are a number of potential advantages for using neoadjuvant chemoradiation. They include the ability to deliver higher doses of chemotherapy with radiation, downstage the tumor, which has been noted in 60–80% of patients, and to achieve a pathologic complete response, which occurs in 15–30% of patients. The ability to 'shrink' the tumor facilitates surgical resection and performs a sphincter-preserving operation, radiating tissues with a greater oxygen supply, and decreases the likelihood of developing radiation enteritis, because the small bowel is less likely to enter the pelvis.
Patients and methods
This study included 80 patients with operable cancer rectum. A total of 40 randomized patients were treated with neoadjuvant chemoradiotherapy (CRT) followed by surgery, and the other 40 patients underwent surgery without neoadjuvant CRT. The pathological response to neoadjuvant CRT with regard to tumor necrosis, size, negative margins, number and size of lymph nodes with operative findings with regard to resectability and blood loss were assessed and then the follow-up of patients was carried out and compared with another group.
Results
We detected a statistically significant difference between both groups with regard to some pathological responses, including grade of tumor differentiation, number and positivity of lymph nodes, perioperative complication, and disease-free survival but no difference in overall survival.
Conclusion
Neoadjuvant chemoradiation could affect the disease-free survival of patients with rectal carcinoma.

Keywords:
neoadjuvant chemoradiation, rectal carcinoma, survival rate

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Introduction

One of the most common human malignancies is colorectal cancer, affecting nearly one million individuals worldwide every year. The annual diagnosis of colorectal cancer is increasing [1].

Accurate preoperative evaluation and staging affect management decisions, allowing identification of patients who should receive neoadjuvant therapy. Advances in the treatment of rectal cancer in the last decade has led to an increase in sphincter-sparing rates and a decrease in local recurrence (Brian *et al.*, [11]).

Definition of neoadjuvant therapy is any form of treatment that the patient receives before a definitive surgical intervention (Påhlman, 2000).

There are a number of potential advantages for using neoadjuvant chemoradiation. They include the ability to deliver higher doses of chemotherapy with radiation. Another advantage is not only to downstage the tumor, which has been noted in 60–80% of patients, but also to achieve a pathologic complete response, which occurs in 15–30% of patients. The ability to 'shrink' the tumor facilitates surgical resection, thereby allowing one to achieve negative margins and perform a sphincter-preserving operation in patients who otherwise would require an abdominoperineal resection (APR). Additional advantages include radiating tissues with a

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greater oxygen supply, not radiating the anastomosis, and decreased the likelihood of developing radiation enteritis because the small bowel is less likely to enter the pelvis. Patients are more likely to complete the course of radiation therapy because it precedes their surgical resection [6].

Neoadjuvant chemoradiotherapy (CRT) could achieve pathologic complete response rates in 3–30% of cancer rectum cases. Combinations of rectal examination, proctoscopy, computed tomography scan, endorectal ultrasound and biopsy are important to assess complete clinical response after treatment, which is present in 7–14% and has been judged by Mark *et al.* [3].

CRT offers downstaging of tumor size, increasing tumor resectability and sphincter-saving surgery. Nowadays, preoperative CRT is accepted as a standard treatment for middle to lower locally advanced rectal cancer. It has been reported to improve local control (Chan AK *et al.*, 2000).

Compared with postoperative CRT, a decrease in local recurrence rate in locally advanced rectal cancer was observed by the use of preoperative CRT (7 vs. 11%; p50.02 in a German randomized trial of 823 patients). Moreover, in resectable rectal cancer, circumferential resection margin involvement was lower in patients receiving preoperative CRT when compared with short course preoperative radiotherapy (4 vs. 13%; p50.017 in a Polish randomized trial of 316 patients) [4].

Patients and methods

After approval of the Menoufia Ethics Committee for the study proposal and between March 2013 and March 2018, this prospective observational study was conducted in Menoufia University Hospitals.

Eighty patients with mid and low cancer rectum were included in our study. We obtained a written informed consent from each patient before enrollment in the trial. They were divided equally into two groups; group A received neoadjuvant chemoradiation and group B underwent surgery without preoperative chemoradiation. Patients with advanced and metastatic cases and old age patients unfit for surgery were excluded from the study.

Each patient was subjected to full history taking, clinical examination, preoperative laboratory and radiological investigations, accurate staging, and colonoscopic assessment, and serum tumor markers CEA and CA 19.9 were used.

Radiotherapy was given to the first group of patients included in the study through Box technique, aiming at the delivery of 45 Gy/25 fractions/5 weeks to the true pelvis and 5.4 Gy/3 fractions as tumor boost. Concomitant Xeloda was given at a dose of 825 mg/m^2 twice daily during radiotherapy days. Evaluation during treatment for acute reactions and toxicity by clinical examination, complete blood picture, renal and liver function tests and other relevant investigations, if indicated, was carried out.

Evaluation of the response 5–6 weeks after the end of treatment by clinical evaluation, MRI pelvis and TRUS, complete laboratory investigations, and using tumor markers CEA and CA 19.9 was carried out.

After the end of chemoradiation in group A by 6–8 weeks, surgery was performed. Type of surgery was determined according to post-treatment disease status, in the form of APR or low anterior resection with preservation of the anal sphincter.

We collected preoperative, operative, postoperative, and outpatient follow up data. Therefter, qualitative data were expressed as number, ratio, or percentage, whereas quantitative variables were expressed as mean and SD. Statistical significance was tested using IBM compatible computer and IBM SPSS statistics, version 19. The significance of the quantitative variable was tested using a paired Student's *t* test. We considered probability values less than 0.05 as statistically significant.

Results

Patients' comorbidities and demographic data showed no significant difference between both groups (Table 1).

Table 1 Comparison between both groups as regards demographic data

	Group		χ^2	*P* value
	Group A (*N*=40)	Group B (*N*=40)		
Sex [*n* (%)]				
Male	24 (60.0)	26 (65.0)	Fisher's exact test 0.104	0.5
Female	16 (40.0)	14 (35.0)		
Age (mean±SD)	57.9±7.08	53.1±12.3	*t* test 1.51	0.139

On comparing both groups, patients receiving neoadjuvant therapy were more likely to have an low anterior resection *n*=26 (65%) versus *n*=16 (40%) and less likely to have an APR (*n*=14, 35% vs. *n*=24, 60%) compared with patients undergoing surgery alone (*P*=0.021), with a statistically significant difference (Table 2).

In addition, in the current study, the operation's time length ranged from 2 to 7 h, with a median of 4 h. Patients receiving neoadjuvant therapy were more likely to have a longer operation time (*P*<0.041) with a statistically significant difference (Table 3).

On comparing both groups, overall morbidity was significantly higher in the group receiving neoadjuvant therapy compared with the surgery alone group (*n*=14, 35% vs. *n*=4, 10%, respectively; *P*=0.031), with a statistically significant difference (Table 4).

On comparing both, moderately differentiated type was present in the majority of the cases in both groups (62 patients) (77.5%). A significant prominent effect of CRT regimen on tumor downstaging was observed for most of the variables. Lymphovascular invasion downstaging was evident and present in 14 (35%) in the no CRT group B compared with only eight (20%) in group A (*P*<0.001), with a statistically significant difference. Positive lymph nodes present in group B were higher in number than those present in group A (3.96±2.4 vs. 2.78±2.4, respectively; *P*<0.001), with a statistically significant difference. Pathologic complete response was shown in four (10%) patients in group A, with a statistically significant difference (Table 5).

Because of the effect of CRT, overall local recurrent rate was decreased in the CRT group, 5% compared with 20% in the no CRT group, respectively. Pathologic stage III in the CRT group showed the highest rate of local recurrence (Table 6).

Discussion

One of the commonest malignancies in humans is rectal carcinoma, and its annual diagnosis is increasing [1].

Careful selection of treatment affects the survival of patients with rectal cancer. Treatment includes surgery, radiotherapy, and chemotherapy as adjuvant or neoadjuvant therapy, which should be integrated according to the primary tumor, regional lymph

Table 2 Comparison between both groups as regards type of surgery

	Group		χ^2	*P* value
	Group A (*N*=40)	Group B (*N*=40)		
Type of surgery performed, APR or LAR [*n* (%)]				
LAR	26 (65.0)	16 (40.0)	Fisher's exact test 11.37	0.021 S
APR	14 (35.0)	24 (60.0)		

APR, abdominoperineal resection; LAR, low anterior resection; S, significance.

Table 3 Comparison between both groups as regards operative time

	Group		χ^2	*P* value
	Group A (*N*=40)	Group B (*N*=40)		
Time of operation [*n* (%)]				
<120	2 (5.0)	10 (25.0)		
120–179	8 (20.0)	8 (20.0)	χ^2 5.9	0.041 S
180–239	10 (25.0)	12 (30.0)		
>240	20 (50.0)	10 (25.0)		

S, significant.

Table 4 Comparison between both groups as regards overall morbidity

	Group		χ^2	*P* value
	Group A (*N*=40)	Group B (*N*=40)		
Morbidity [*n* (%)]				
Yes	14 (35)	4 (10)	Fisher's exact test 10.99	0.031 S
No	26 (65)	36 (90)		

S, significant.

Table 5 Comparison between both groups as regards pathological response

Histology	A CRT (*N*=40)	B No CRT (*N*=40)	*P* value
Total LN (mean±SD)	15.45±8.6	22.73±13.2	0.001 HS
Positive LN (mean±SD)	2.78±2.4	3.96±2.4	0.001 HS
Lymphovascular invasion [*n* (%)]			
No	32 (80)	26 (65)	0.001 HS
Yes	8 (20)	14 (35)	
Pathologic tumor depth stage [*n* (%)]			
T0, 1, 2	18 (45)	12 (30)	0.001 HS
T3, 4	22 (55)	28 (70)	
Cell differentiation [*n* (%)]			
Well differentiated	6 (15)	2 (5)	0.257 NS
Moderately differentiated	30 (75)	32 (80)	
Poorly differentiated	4 (10)	6 (15)	
Pathologic complete response			
No	36 (90)	40 (100)	0.001 HS
Yes	4 (10)	0 (0)	

CRT, chemoradiotherapy; HS, highly significant; S, significant; LN, lymph nodes.

Table 6 Comparison between both groups as regards disease-free survival

	Group		χ^2	*P* value
	Group A (*N*=40)	Group B (*N*=40)		
Recurrence [*n* (%)]				
L	2 (5)	8 (20)	10.2	0.023 S
S	2 (5)	10 (25)		
No	36 (90)	22 (55)		

S, significant.

nodes, and distant metastasis. Consideration of these parameters causes an improvement in local control and disease-free survival [2].

Many factors affect the prognosis of cancer rectum, including TNM stage, lymphatic invasion, vascular invasion, pathologic type, and resection margins [3].

Starting with neoadjuvant chemoradiation in the treatment plan of patients with rectal cancer may offer downstaging effect and improve local control rate. The local recurrence rate stage II–III rectal cancer, even if resectable, was 15–65% [4].

Thus, for resectable stages II and III, using preoperative chemoradiation therapy is the standard treatment, and it is also the only standard treatment for the locally advanced disease. It can reduce tumor size and bulk, allowing more preserving surgery and decreases dissemination of the tumor during surgery [5].

Many clinical trials such as FFCD 92-03 and EORTC 22921 studied the effect of neoadjuvant chemoradiation and recommend it for the treatment of stages II and III rectal cancer [6].

Patients with resectable disease who received neoadjuvant chemoradiation, especially those who achieved a complete pathological response, showed better control rate but failed to show improvement in overall survival rate [7].The recommended treatment for stages II and III cancer rectum is preoperative chemoradiation, surgery with total mesorectal excision plus systemic chemotherapy [8].

Furthermore, tumor location is considered as a prognostic factor in a phase III randomized study in the Netherlands, as neoadjuvant chemoradiation affects middle and low rectal tumor more than high rectal cancer [9].

Sphincter-preserving surgery is affected by the distance of tumor to anal verge and response to neoadjuvant chemoradiation. Significant predictors for local recurrence are positive circumferential margin, infiltration beyond serosa, and lymph node metastasis [10].

Conclusion

Neoadjuvant chemoradiation therapy, although associated with higher morbidity, affects disease-free survival, with no affection for overall survival in rectal cancer, it may affect survival in the patient who achieves complete pathological response.

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Conflicts of interest

There are no conflicts of interest.

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