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ORIGINAL ARTICLE

Treatment Outcome of Locally Advanced Rectal Cancer

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Abstract

Background: **Colorectal cancer is the third commonest cancer worldwide. Most cases presented with locally advanced stage.**

Objective: **To analyze treatment outcome, disease-free survival (DFS), and overall survival (OS) of patients with locally advanced rectal adenocarcinoma.**

Patients and methods: **This retrospective study included patients with stages II and III rectal adenocarcinoma referred to El-Hussein University Hospital during the period between June 2016 and January 2020, with analysis of their personal and disease-related data.**

Results: **A total of 66 patients were included; 57 of them received preoperative short-course radiotherapy (SCRT) or concurrent chemoradiotherapy (CCRT), and 42 of them were subjected to curative surgery. The rate of pathological complete remission (pCR) in SCRT and CCRT was 15.1 and 22.3%, respectively ($P = 0.7$), and pCR was associated with 100% OS at 3 years. Median OS for SCRT and CCRT groups was 3.7 and 3.5 years, respectively ($P = 0.53$). The cumulative OS at 1 and 3 years in CCRT and SCRT groups was 90.6 and 80.8%, and 97.2 and 68.5%, respectively. Of 66 patients, nine received postoperative CCRT. Median OS and DFS for preoperative group was 3.6 and 1.1 years, respectively.**

Conclusion: **There was no statistically significant difference between preoperative and postoperative CCRT, or between preoperative SCRT and CCRT with delayed surgery in both, regarding DFS and OS. It is suggested that patients with pCR might have better DFS and OS.**

Keywords: Concurrent chemoradiotherapy, Pathological complete remission, Rectal adenocarcinoma, Short-course radiotherapy

1. Introduction

Colorectal cancer is the third commonest cancer worldwide; moreover, it is the second most common cause of cancer-related death. In Egypt, colorectal cancer is the seventh commonest cancer[1] with increased incidence toward young people associated with worse prognosis.[2,3] Most cases usually presented with advanced stage,[4] and the most affected anatomical part is the low rectum.[5]

MRI rectal protocol is the gold standard for local disease evaluation and consequently can determine the optimal treatment regimen.[6] Moreover, MRI contributes in the delineation of target volumes in radiotherapy setting, as radiotherapy gained importance after publishing of NSABP protocol R-01.[7] The importance of preoperative radiotherapy represented in improving local control, and this was shown in studies that compared preoperative concurrent chemoradiotherapy (CCRT) with postoperative CCRT.[8]

Total neoadjuvant became a standard of care for patients with locally advanced rectal adenocarcinoma since the RAPIDO and the PRODIGE 23 trials were revolutionized in ASCO 2020.[9] Despite that, mesorectal surgical resection remains an integral

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part of curative therapy for this disease,[10] as watch and wait strategy still has controversy.[11]

Immunotherapy was investigated in neoadjuvant setting, as d-MMR patients with locally advanced rectal adenocarcinoma were enrolled in phase II trial to receive anti PD-1 agent, and all of them had a clinical complete response.[12]

Worldwide, the 1- and 5-year net survival varied between 84.8 and 90.0% and between 61.6 and 70.9%, respectively, for rectal adenocarcinoma.[13]

The aim of work of this retrospective study was to analyze treatment outcome, disease-free survival (DFS), and overall survival (OS) for patients with locally advanced rectal adenocarcinoma.

2. Patients and methods

This retrospective study included patients with a pathologically confirmed diagnosis with rectal adenocarcinoma, referred to Clinical Oncology and Nuclear Medicine Department, El-Hussein University Hospital, Faculty of Medicine, Al-Azhar University, Cairo, during the period between June 2016 and January 2020. Data of patients were collected from files in the archive.

2.1. Selection criteria

Patients with age more than 18 years and less than 80 years of both sexes, who were histopathologically proven to have rectal adenocarcinoma, that is, clinically or pathologically locally advanced rectal adenocarcinoma stages II and III according to AJCC staging system 8th edition, were included.

2.2. Exclusion criteria

Patients with stage IV disease, tumors extending above 15 cm from the anal verge, and patients with synchronous malignancies were excluded.

2.3. Methods

The following data were collected: patient-related data such as age, sex, performance status, and associated comorbidities; disease-related data such as site of the disease, histopathology, grade, clinical stage at presentation, and pathological stage after surgery; treatment-related data such as radiotherapy (dose/fractions and technique), chemotherapy regimen, surgery (type and complications), and treatment related toxicity; and treatment outcome-related data, such as post neoadjuvant clinical outcome according to Revised RECIST guideline (version 1.1), post neoadjuvant pathological outcome after surgery by Modified Ryan's tumor regression grade, pattern of relapse, DFS, and OS.

One-sided log-rank Kaplan–Meier survival estimates were used for statistical analysis of overall survival and disease-free survival, whereas the unpaired *t* test and one-way analysis of variance test were used in the univariate analysis of the variables.

3. Results

From June 2016 to Jan 2020, 66 patients were diagnosed with locally advanced rectal adenocarcinoma. Of 66 patients, 57 (86.3%) presented with clinically locally advanced disease either stage II or stage III, whereas nine (13.7%) patients presented after surgery with pathologically stage II or stage III. The age at the time of diagnosis ranged between 22 and 77 years. The mean age was 49.51 years. Of 66 patients, 34 (51.5%) were diagnosed at age less than 50 years. Regarding sex, 28/66 (42.4%) patients were males, whereas 38/66 (57.5%) patients were females, with male to female ratio of 1 : 1.3. A total of 16 (24.2%) patients had the habit of smoking, with no statistically significant difference between smokers and nonsmokers regarding OS (hazard ratio = 0.65; 95% confidence interval: 3.3–5.2, $P = 0.271$). Overall, 11 (16.6%) patients have had a first-degree relative family history of colorectal cancer (Table 1).

3.1. Treatment-related data

The preoperative group of 57 patients underwent neoadjuvant treatment by either short-course radiotherapy (SCRT) (25 Gy/5 fractions with daily DRR) followed by surgery after 4–8 weeks or CCRT (50.4 Gy/28 fractions) with capecitabine (825 mg/m^2 BID) followed by surgery after 6–8 weeks. There were 8/57 (14%) patients who missed or were referred to another center before starting SCRT, 38/57 (31.5%) patients finished SCRT, and 11/57 (19.2%) patients finished CCRT. However, postoperative group of nine patients was subjected to postoperative CCRT (50.4 Gy/28 fractions) with capecitabine (825 mg/m^2 BID) followed by 4 months of folfox.

Regarding radiotherapy technique for preoperative group, 46/57 (80.7%) patients received radiotherapy by IMRT technique, whereas 3/57 (5.3%) patients received radiotherapy by three DCRT technique. On the contrary, all patients of postoperative group (9/9 patients) received three DCRT. Regarding radiotherapy-related toxicity, proctitis was the most frequent complications associated with radiotherapy. CCRT was associated with a higher incidence of grades 3 and 4 toxicity in comparison with SCRT, and there was a statistically

Table 1. Patient-related data and disease-related data.

Personal and disease criteria	Preoperative group ($N = 57$) [n (%)]		Postoperative group ($N = 9$)
Description	SCRT ($N = 46/57$)	CCRT ($N = 11/57$)	
Sex			
Male	20 (43.4)	5 (45.4)	3 (33.3)
Female	26 (56.5)	6 (54.5)	6 (66.6)
Age (years)			
Mean ± SD	49.51 ± 14.51	49.4	43.2 ± 9.3
Median	52.0	51.5	45
Range	22–77	22–57	
Age categories (years)			
<50	24 (52.1)	4 (36.4)	8 (88.8)
≥50	22 (47.8)	7 (63.6)	1 (11.1)
Family history			
No	40 (86.9)	8 (72.7)	7 (77.7)
Yes	6 (13.1)	3 (17.3)	2 (22.2)
Smoking			
No	36 (78.2)	7 (63.6)	8 (88.8)
Yes	10 (21.8)	4 (63.6)	1 (11.1)
Comorbidities			
No	26 (56.5)	6 (54.5)	6 (66.6)
Yes	20 (43.4)	5 (45.4)	3 (33.3)
PS (ECOG)			
0	8 (17.3)	2 (18.1)	1 (11.1)
1	27 (58.6)	8 (72.7)	8 (88.8)
2	11 (23.9)	1 (9.2)	0
Initial tumor marker			
Normal	7 (15.2)	9 (81.9)	2 (22.2)
High	39 (84.7)	2 (18.1)	7 (77.7)
Site			
Low	30 (65.2)	3 (17.3)	3 (33.3)
Middle	12 (26)	8 (72.7)	6 (66.6)
High	4 (8.8)	0	0
Grade			
1	4 (8.8)	0	0
2	28 (60.8)	10 (90.8)	7 (100)
3	14 (30.4)	1 (9.2)	2 (22.2)
T stage			
T2	11 (23.9)	0	0
T3	35 (76.1)	11 (100)	9 (100)
N stage			
N0	6 (13.1)	2 (18.1)	2 (22.2)
N1	25 (54.3)	8 (72.7)	5 (55.6)
N2	15 (32.6)	1 (9.2)	2 (22.2)

CCRT, concurrent chemoradiotherapy; SCRT, short-course radiotherapy.

significant difference between SCRT and CCRT regarding associated toxicity.

Regarding surgical management, in preoperative group, 42/57 (73.6%) patients underwent surgery, where 25/42 (59.6%) patients underwent low anterior resection (LAR), whereas 17/42 patients (40.4%) underwent abdominoperineal resection (APR). On the contrary, 13/57 (22.8%) were not subjected to surgery, either due to missing or referred to another center before starting treatment or due to progression on neoadjuvant treatment, whereas 2/57 (3.5%) patients were irresectable.

Postoperative complications like delayed wound healing, DVT, or fistula were noticed in 15/42 (35.7%) patients, with no statistically significant difference between SCRT and CCRT regarding postoperative complications ($P = 0.16$).

Regarding postoperative group, 3/9 patients were subjected to LAR, whereas 6/9 were subjected to APR, with no documented postoperative complications.

Concerning adjuvant chemotherapy, 21/57 (36.8%) patients received adjuvant folfox, whereas 19/57 (33.3%) patients received xelox and 3/57 received Mayo clinic regimen, without statistically significant difference regarding OS ($P = 0.31$).

Regarding toxicity of adjuvant chemotherapy, we realized that patients who received CCRT developed higher incidence of grades 3 and 4 toxicity with adjuvant chemotherapy than patients who received SCRT (Tables 2–4).

Table 2. Radiotherapy technique and toxicity-related data.

	Preoperative ($N = 49/57$)*			P value	Postoperative ($N = 9$)	P value
Technique of radiotherapy	3DCRT 3/49 CCRT 3/3	IMRT 46/49 SCRT 38/46	CCRT 8/46		3DCRT 9/9 CCRT 9/9	
OAR						
Bowel mean dose						
Mean	27.9	10.6			24.8	
Median	30	6.7			28	
Bladder mean dose						
Mean	44.2	23.6			38.8	
Median	44	21.5			39	
Right femur						
Mean	24.8	12.5			23.7	
Median	25.2	11			22.6	
Left femur						
Mean	26.1	12.3			22.8	
Median	28.07	10.4			22.4	
Toxicity						
Cystitis [n (%)]						
No	0	35 (92.1)	2 (25)	0.00051	3 (33.3)	0.09
Yes	3 (100)	3 (7.9)	6 (75)		6 (66.7)	
Proctitis [n (%)]						
No	0	35 (92.1)	1 (12.5)	0.00022	9 (100)	0.4
Yes	3 (100)	3 (7.9)	7 (87.5)		0**	
Neuropathy grades 3, 4 [n (%)]						
No	1 (33.4)	38 (100)	4 (50)	0.004	6 (66.7)	
Yes	2 (66.6)	0	4 (50)		3 (33.3)	
Hematological grades 3, 4 [n (%)]						
No	1 (33.4)	38 (100)	6 (75)	0.0006	7 (77.7)	0.2
Yes	2 (66.6)	0	2 (25)		2 (22.3)	

CCRT, concurrent chemoradiotherapy; SCRT, short-course radiotherapy.

3.2. Treatment outcome-related data

Post neoadjuvant clinical response assessment through MRI and colonoscope is considered a significant prognostic factor. Table 7 shows that 27/49 (55.2%) patients achieved partial response, 5/49 (10.2%) patients developed progressive disease, and 11/49 (22.4%) patients had stable disease. On the contrary, 6/49 (12.2%) patients achieved clinical complete remission (Table 5).

We can realize that all patients who achieved clinical complete remission have significant survival benefit, as the 3-year survival for patients who achieved clinical complete remission, partial response, and progressive disease was 100, 68, and 41%, respectively.

Regarding recurrence, we found that during the follow-up period, 25/51 (49%) patients developed recurrence, and the pattern of recurrence was mostly local recurrence in 16/51 (31.3%) patients (Table 6).

Comparing the used two modalities in neoadjuvant treatment for rectal adenocarcinoma, SCRT and CCRT, about 38/49 (77.5%) patients received SCRT, whereas 11/49 (22.4%) patients received CCRT. On the contrary, there was no statistically significant difference between the two modalities regarding clinical response after neoadjuvant treatment, as shown in Table 7.

Pathological outcome was shown in Table 7, as 9/42 (21.4%) patients achieved partial response, 3/42 (7%) patients developed poor response outcome, and 23/42 (54.7%) patients had near-complete remission. On the contrary, 7/42 (16.6%) patients achieved pathological complete remission (pCR).

We can realize that all patients achieved pCR have significant survival benefit. Hence, the 3-year survival for patients who achieved pCR, near complete remission, and poor response was 100, 72, and 67%, respectively.

Comparing the used two modalities in neoadjuvant treatment for rectal adenocarcinoma, SCRT and CCRT,

Table 3. Types of surgery and related complications.

	Preoperative group ($N = 42/57$) [n (%)]		P value	Postoperative group ($N = 9$)
	SCRT 33/33	CCRT 9/9		N (100%)
Type of surgery				
APR	17 (51.5)	0		6 (33.3)
LAR	16 (48.5)	9 (100)		3 (66.7)
Complications				
No	24 (72.7)	3 (33.3)	0.16	–
Yes	9 (27.3)	6 (66.7)		–

APR, abdominoperineal resection; CCRT, concurrent chemoradiotherapy; LAR, low anterior resection; SCRT, short-course radiotherapy.

Table 4. Adjuvant chemotherapy and related toxicity.

Adjuvant chemotherapy	Preoperative ($N = 42/57$) [n (%)]			Postoperative ($N = 9$)
	SCRT (33)	CCRT (9)	P value	n (%)
Type of protocol				
FOLFOX	20 (60.6)	1 (11.1)		9 (100)
Mayo clinic regimen		3 (9.1)	0	0
XELOX	10 (30.3)	8 (88.9)		0
Toxicity grades 3, 4				
Neuropathy				
Yes	6 (18.1)	3 (33.3)	0.01**	2 (22.2)
No	27 (81.9)	6 (66.7)		7 (77.8)
Diarrhea				
Yes	8 (24.2)	2 (22.2)	0.73	1 (11.1)
No	25 (75.8)	7 (77.8)		8 (88.9)
Nausea/vomiting				
Yes	4 (12.2)	3 (33.3)	0.01**	1 (11.1)
No	29 (87.8)	6 (66.7)		8 (88.9)
Hematological grade 3, 4				
Yes	10 (30.3)	5 (55.5)	0.01**	2 (22.2)
No	23 (69.7)	4 (44.5)		7 (77.8)

CCRT, concurrent chemoradiotherapy; SCRT, short-course radiotherapy.

there was no statistically significant difference between the two modalities regarding pathological response after neoadjuvant treatment, as shown in Table 7.

Regarding surgery, there was also no statistically significant difference between APR and LAR regarding local or distant recurrence.

The OS of studied patients was measured and had a median of 3.7 years for patients who received SCRT and 3.5 years for patients who received CCRT. There was no statistically significant differences between the two treatment modalities regarding OS ($P = 0.53$). The 1- and 3-year survival of patients who received CCRT was 90.6 and 80.8%, respectively, whereas in patients who received SCRT was 97.2 and 68.5%, respectively.

Regarding DFS at a median follow-up of 1.2 years, there was no statistically significant difference between SCRT and CCRT regarding DFS ($P = 0.522$), and the DFS was 62 and 65%, respectively.

Regarding preoperative and postoperative treatment, there was no statistically significant difference regarding DFS and OS.

The median OS for preoperative group was 3.6 years, whereas median OS for postoperative group was not reached.

Table 5. Post neoadjuvant treatment clinical and pathological outcome among the studied patients.

Outcome	Preoperative group ($N = 49/57$) [n (%)]		
	SCRT 38	CCRT 11	P value
Post neoadjuvant clinical outcome			
Complete response	5 (13.1)	1 (9.1)	0.68
Partial response	20 (52.6)	5 (45.4)	0.54
Progressive disease	3 (7.8)	2 (18.2)	0.32
Stable disease	10 (26.3)	2 (18.2)	0.24
	SCRT 33	CCRT 9	
Pathological outcome			
Complete response	5 (15.1)	2 (22.3)	0.7
Near complete response	18 (54.5)	5 (55.5)	0.9
Poor or no response	2 (6)	1 (11.1)	0.2
Partial response	8 (24.4)	1 (11.1)	0.8

CCRT, concurrent chemoradiotherapy; SCRT, short-course radiotherapy.

4. Discussion

Egypt faces increased incidence of locally advanced rectal cancer in young population, which is associated with worse prognosis and aggressive behavior.[14] Recently, total neoadjuvant therapy became a standard of care for patients with locally advanced rectal cancer, to induce down staging, sphincter preservation, local control, and even pCR.[9] Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial after a median follow-up of 11 years showed that preoperative CCRT was better than postoperative CCRT regarding local control, with no statistically significant difference regarding OS.[8]

In our retrospective study, there was no statistically significant difference between preoperative CCRT and postoperative CCRT regarding DFS and OS.

The two phase III trials 'Polish' and 'TROG 0104' have compared SCRT alone versus CCRT. They failed to show statistically significant differences regarding local recurrence rate, DFS, and early/late toxicities, but they showed significant pCR, in the arm containing patients who received CCRT.[15]

Table 6. Distribution of the studied patients regarding recurrence.

	Preoperative group ($N = 42/57$) [n (%)]		P value	Postoperative group 9 [n (%)]	P value
	SCRT 33	CCRT 9		CCRT	
Site of recurrence					
Local					
Yes	11 (33.3)	2 (22.2)	0.6	3 (33.3)	0.9
No	22 (66.7)	7 (87.8)		6 (66.4)	
Liver					
Yes	5 (15.5)	2 (22.2)	0.20	1 (11.2)	0.7
No	28 (84.5)	7 (87.8)		8 (88.8)	
Lung					
Yes	1 (3)	0	0.62	0	0.3
No	32 (97)	9 (100)		9 (100)	

CCRT, concurrent chemoradiotherapy; SCRT, short-course radiotherapy.

Table 7. Site of recurrence in patients treated with difference surgeries.

	LAR (28/51)	APR (23/51)	P value
Local			
Yes	7 (25)	9 (39)	0.4
No	21 (75)	14 (61)	
Liver			
Yes	3 (12)	5 (27.7)	0.20
No	22 (88)	13 (72.3)	
Lung			
Yes	1 (4)	0	0.62
No	24 (96)	18 (100)	

APR, abdominoperineal resection; LAR, low anterior resection.

Our retrospective study showed that there was no statistically significant difference between SCRT and CCRT regarding OS ($P = 0.53$). The 1- and 3-year survival of patients who received CCRT was 90.6 and 80.8%, respectively, whereas in patients who received SCRT was 97.2 and 68.5%, respectively.

Stockholm III trial reported severe acute toxicity in less than 1% of the patients receiving SCRT with immediate surgery group, 4.2% of the patients in SCRT with delayed surgery group, and 5% in the CCRT group, and it was thought that acute radiation toxicity was masked by surgical complications in the SCRT with immediate surgery group.[16]

In our study, we realized that patients who received SCRT developed less toxicity than patients who received CCRT, with statistically significant difference.

It is suggested that patients with pCR might have better DFS and OS, as reported by Abdel-Rahman *et al.*[16] and this is shown in our study, as patients who achieved pCR had better OS and DFS than who did not achieve pCR.

A retrospective study from the Netherlands found that there was a statistically significant pCR achieved by CCRT in comparison with SCRT. The incidence of pCR was 17.5 and 9.3%, respectively. Moreover, Stockholm III trial reported a pCR rate of 11.8% in patients receiving SCRT with delayed surgery.[16]

In our study, there was no statistically significant difference between the two modalities regarding pCR, as patients who received SCRT achieved 13.1% rate of pCR, whereas patients who received CCRT achieved 18.18% rate of pCR ($P = 0.7$).

Regarding postoperative complications, the Polish trial demonstrated that the rates of postoperative complications for the SCRT with immediate surgery group and the long course CCRT group were 27 vs. 21%, respectively, but it was noticed that only 39% of the patients were subjected to APR.[15]

In our study, ~37.7% of patients developed postoperative complications, with no statistically difference between SCRT and CCRT.

Regarding adjuvant chemotherapy protocols, there was no randomized trial comparing folfox versus xelox as postoperative adjuvant chemotherapy. In our study, we found that there was no statistically significant difference between folfox and xelox regarding OS ($P = 0.31$).

4.1. Conclusion

Despite the small number of patients in this study, it is suggested that patients with pCR might have better DFS and OS. There was no statistically significant difference between preoperative and postoperative CCRT or between SCRT and CCRT with delayed surgery in both, regarding DFS and OS.

Ethical approval and consent statement

An ethical approval from the formally constituted review board of the clinical oncology department was done. On the other hand, written consents were obtained from patients who were included in the study.

Conflict of interest

Authors declare that there is no conflict of interest, no financial issues to be declared.

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