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Original article

Outcomes of Preoperative *versus* Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer

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Abstract

Aim*. To investigate the patients' outcomes of preoperative chemoradiotherapy (CRT) versus postoperative CRT for locally advanced rectal cancer.* ***Patients and Methods****. Clinicopathological variables of 124 patients with locally advanced rectal cancer treated with CRT preoperatively (81 patients) or postoperatively (43 patients) from 2010 to 2017 was investigated retrospectively.* ***Results****. There was no significant differences of patients' characteristics between two groups. Through follow-up duration 52 months (range, 7-116 months), 24 patients (34.6%) in the preoperative CRT group and 28 patients (55.8%) in the postoperative CRT group had died. The 5-year overall survival rate was 65.3% and 34.7% for the preoperative and postoperative CRT group, respectively (p = 0.010). The 5-year disease free survival rate was 85.3% and 53.5% for the preoperative and postoperative CRT group, respectively (p = 0.007). Pathologic tumor and nodal down-staging observed after the preoperative CRT with statistically significance (p <0.0001 and p <0.0001, respectively). Postoperative CRT group had higher ratio of adverse events than preoperative CRT (46.5 % and 21%, respectively).* ***Conclusion****. In patients with locally advanced rectally cancer, preoperative CRT could be advantageous for improving overall survival, disease free survival, tumour regression rate and to reduce adverse events.*

Keywords: *Locally Advanced Rectal Cancer, Chemoradiotherapy, Preoperative, Postoperative, Patients' Outcomes.*

Introduction

Globally, colorectal cancer (CRC) is the third most common type of cancer and the second cause of cancer related death [1]. In 2018, there were more than one million new cases and 550,000 deaths from the disease [2]. CRC is known as bowel cancer or rectal cancer, is the development of cancer from the colon or rectum [3]. Rectal cancer is considered when the primary tumour located through 12 cm from anal verge [4].

Preoperative chemoradiotherapy (preoperative CRT) followed by radical surgery and adjuvant chemotherapy has become the standard treatment for locally advanced rectal cancer (stage II and/or III) [5]. Preoperative CRT is effective to improve local control, overall survival and tumour regression [6, 7 and 8]. Tumour regression such as down staging and pathologic complete response of primary tumour after preoperative CRT are considered as prognostic factors in rectal cancer [9, 10 and 11].

The preoperative CRT could be is a better treatment than postoperative CRT to enhance the rate of tumour regression, local control, and sphincter preservation and to reduce the risk of adverse events [8 and12]. Anyhow, there is still debate over regarding improves overall survival in locally advanced rectal cancer patients treated with preoperative CRT and surgery [13, 14 and 15]. Nearly one-third of patients had distant metastasis despite treatment with preoperative CRT and surgery [16].

The aims of this study was to investigate the patient's outcomes of preoperative versus postoperative CRT for locally advanced rectal cancer.

Patients and methods

Study design and patient's characteristics

A total of 124 Libyan patients with locally advanced rectal cancer who received preoperative CRT (81 patients) or postoperative CRT (43 patients) were studied retrospectively. All patients were diagnosed and treated between 2010 and 2017 at the National Cancer Institute in Misurata, Libya.

Standardized rectal cancer Magnetic Resonance Imaging (MRI) was performed in all patients to assess tumour extension [17]. Eligibility criteria include histologically confirmed rectal cancer, clinically or pathologically diagnosed stage II (T3 or T4 without any lymph node involvement) and/or stage III (any tumor stage with positive lymph node), and without distant metastasis. Patients with double primary malignancy and incomplete follow-up were excluded.

The clinicopathological variables such as age, gender, histologic grade, tumour location, preoperative and postoperative clinical staging, pathologic staging, adverse events of treatment, relapse (local and/or metastasis), serum levels of carcinoembryonic antigen (CEA), type of treatment and follow-up data were collected. The clinicopathological variables of patients are shown in Table 1.

Table 1. Patient characteristics

Variables	Threshold	No of patients	Chemoradiotherapy arm		
			Preoperative CRT (n=81) N (%)	Postoperative CRT (n=81) N (%)	P value
Age /years	< 50	39	24 (61.5)	15 (38.5)	0.550
	≥ 50	85	57 (67.1)	28 (32.9)	
Gender	Male	72	50 (69.4)	22 (30.6)	0.258
	Female	52	31 (59.6)	21 (40.4)	
Tumour site from anal verge/ cm	<5	32	22 (68.8)	10 (31.2)	0.634
	≥5	92	59 (64.1)	33 (35.9)	
CEA ng/ml	< 5	63	38 (60.3)	25 (39.7)	0.233
	≥ 5	61	43 (70.5)	18 (29.5)	
Histological grade	Grade I	13	5 (38.5)	8 (61.5)	0.088
	Grade II	81	57 (70.4)	24 (29.6)	
	Grade III	31	19 (63.3)	11 (36.7)	
Clinical tumour stage	T1	0	0 (00.0)	0 (00.0)	0.445
	T2	4	3 (75.0)	1 (25.0)	
	T3	97	62 (63.9)	35 (36.1)	
	T4	23	16 (69.6)	7 (30.4)	
Clinical nodal stage	Positive	83	51 (61.4)	32 (38.6)	0.192
	Negative	41	30 (73.2)	11 (26.8)	
Recurrence	Yes	41	20 (48.8)	21 (51.2)	0.007
	No	83	61 (73.5)	22 (26.5)	

CRT, chemoradiotherapy; CEA, carcinoembryonic antigen.

Tumour staging of rectal was evaluated according to the American Joint Committee on Cancer (AJCC), TNM classification [18]. Pan-colonoscopy and radiological staging by Computed Tomography (CT) and/or MRI was performed in all patients to assess tumour extension. The extent of the tumour (local and/or metastasis) at the time of diagnosis was confirmed by imaging [CT, MRI, or Positron Emission Tomography (PET)]. Primary tumour considered as rectal cancer if it was located through 12 cm from anal verge [4]. Blood samples from the patients were analyzed for CEA levels before treatment by electrochemiluminescence immunoassay and CEA level equal or higher than 5 ng/ml was considered abnormal.

Treatment and follow-up

Patients diagnosed with locally advanced rectal cancer were either treated with preoperative CRT followed by radical surgery or radical surgery followed by CRT. Radiotherapy was given at 45 Gy in 25-28 fractions over the course of 5 weeks, preoperatively and postoperatively for both groups. During radiation treatment, intravenous 5-fluorouracil (425 mg/m2) and leucovorin (20mg/m2) were given as bolus on weeks 1 and 5, or orally capecitabine 1,650mg twice daily throughout radiation therapy. Adjuvant chemotherapy regimen based on FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and/or XELOX (oxaliplatin and capecitabine) over the course of 6 months was given to patients. All patients underwent radical surgery. Surgical resection was performed at median 8 weeks (range, 5 to 12 weeks) after completion of radiotherapy in the preoperative CRT group.

Follow-up of patients was carried out every 3 months for 2 years, 6 months for 5 years, and thereafter every 1 year. Disease recurrence (local and distant metastases) was confirmed by colonoscopy and imaging (CT, MRI, or PET) performed when clinical symptoms suggestive of disease recurrence were present. Patients outcomes were considered as follows: overall survival (OS), duration between the date of pathological diagnosis to the date of death and/or to date of the end follow up period; disease-free survival (DFS), duration between the date of pathological diagnosis to the date of diagnosis of recurrence (local and/or distant metastases) or death [19].

Patients were followed up until death or to the end of the observation period (until December 2021). The median follow-up duration was 52 months (range, 7-116 months).

Statistical analysis

Data of all categorical variables are summarized using frequencies and percentages. Frequency tables were analysed using the Chi-square test, with likelihood ratio (LR) to assess the significance of the correlation between the categorical variables. Kaplan Meier with log-rank test was used to analyze survival difference between the two groups. Disease free survival was defined as the time interval between surgery and tumor recurrence or last follow-up. Overall survival was defined as the time interval between the surgery and death or last follow-up. When a P-value was less than 0.05, the difference was considered significant. SPSS 26.0 statistical software was used for data analysis.

Ethical approval

The study was approved by ethical committee at the National Cancer Institute, Misurata. Written informed consent was obtained from all patients for surgical treatment, pathologic examinations and research work.

Results

Patient Characteristics

Between January 2010 to December 2017, a total of 170 patients were diagnosed with rectal cancer in the National Cancer Institute, Misurata, Libya. After excluding patients who had metastasis (n=22), double primary malignancy (n=3), and loss of follow up (n=21), data of 124 patients [preoperative CRT, n=81 (65.3%); postoperative CRT, n=43 (34.7%)] were collected Figure 1.

Clinicopathological characteristics such as age, gender, histologic grade, clinical stage, CEA level, tumour location and risk of recurrence were balanced between the two groups (Table 1). There was no significant difference between the preoperative and postoperative CRT group with exception of the risk of recurrence. The ratio of patients how had no recurrence (local and metastasis) was higher in the preoperative CRT group than postoperative CRT group (73.5% vs. 26.5% respectively, p = 0.007).

Tumor Characteristics

A significant down staging of pathologic stage was observed in the preoperative CRT group. In this group, 7 patients had a complete response (pT0) and 47 patients with negative lymph nodes ($p<0.0001$). Moreover, preoperative CRT group had higher proportion of stage I (n=33, 91.7%) and lower rate of stage III (n= 17, 37%) compare to the postoperative CRT group of stage I (n=3, 8.3%) and stage III (n=29, 63%, $p<0.0001$) respectively Table 2.

Figure 1. Study scheme

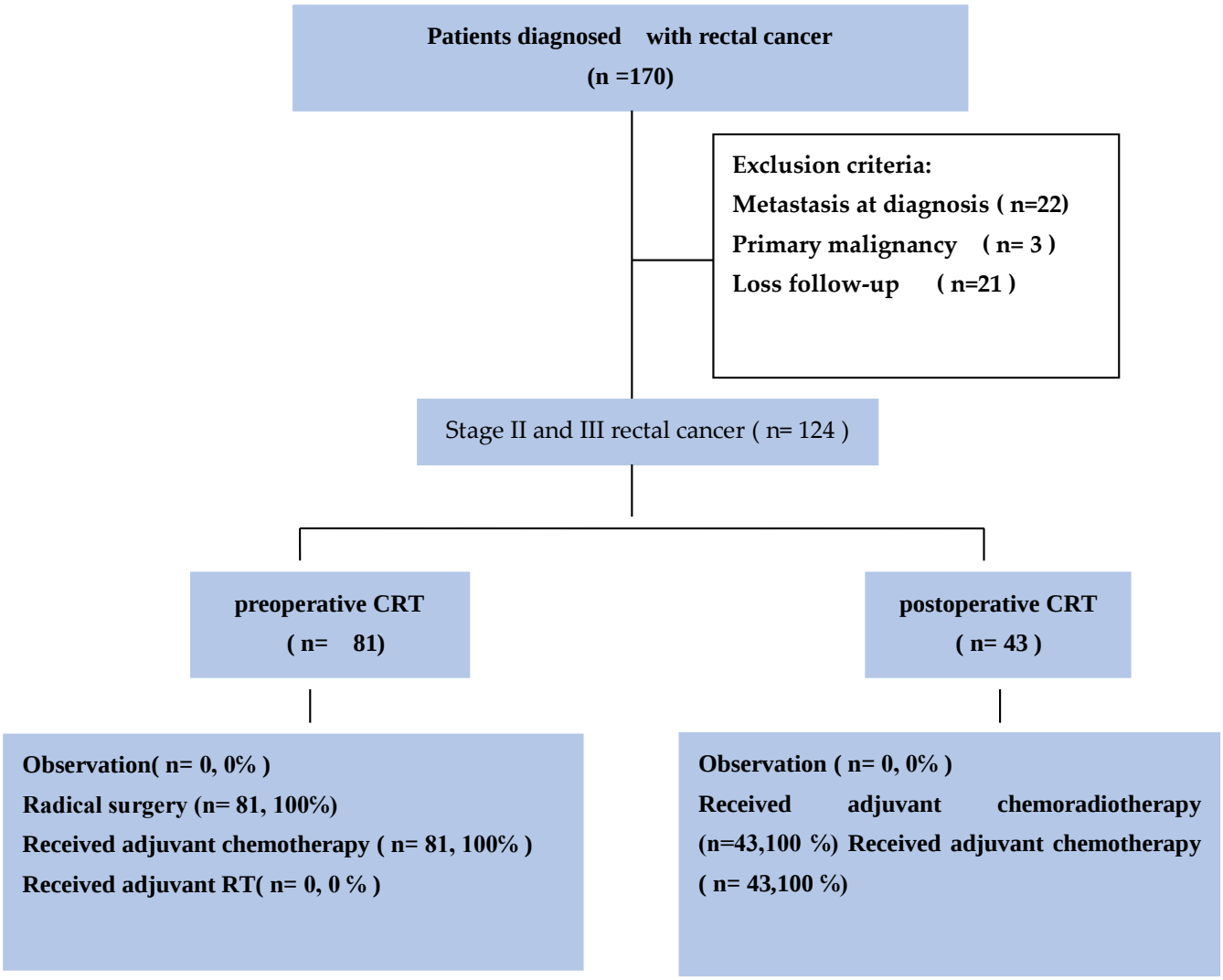

Figure 2. (A and B). A. Overall survival of 124 Libyan patients with rectal cancer who received preoperative or postoperative chemoradiotherapy (CRT). B. Disease-free survival of 124 Libyan patients with rectal cancer who received preoperative or postoperative chemo-radiotherapy (CRT).

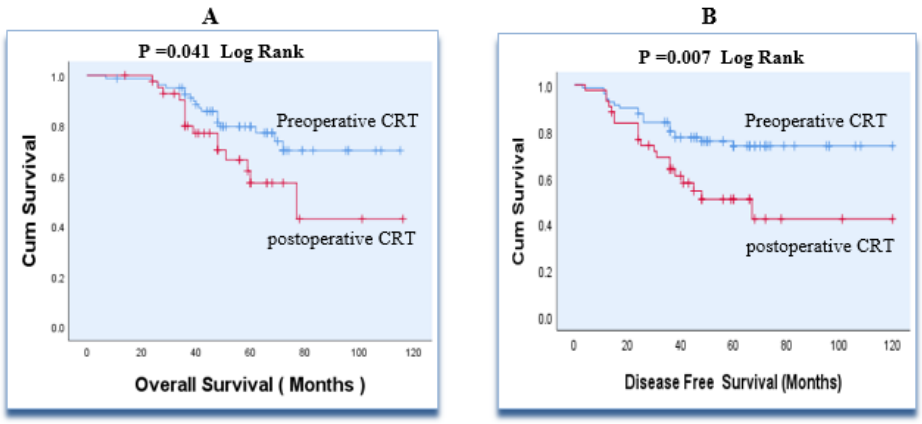

Table 2. Pathologic tumor and nodal stage in both treatment groups

Variables	Threshold	No of patients	Preoperative CRT (n=81) N (%)	Postoperative CRT (n=43) N (%)	P value
Tumor stage	pT0	7	7 (100)	0 (00.0)	**<0.0001**
	pT1	16	16 (100)	0 (00.0)	
	pT2	32	30 (93.8)	2 (6.2)	
	pT3	62	28 (45.2)	34 (54.8)	
	pT4	7	0 (00.0)	7 (100)	
Nodal stage	pN0	58	47 (81.0)	11 (19.0)	**<0.0001**
	pN1	48	26 (61.9)	16 (38.1)	
	pN2	24	8 (33.3)	16 (66.7)	
Pathologic stage	Stage I	36	33 (91.7)	3 (8.3)	**<0.0001**
	Stage II	42	31 (73.8)	11 (26.2)	
	Stage III	46	17 (37.0)	29 (63.0)	

CRT, Chemoradiotherapy.

Patients Outcomes: Overall Survival and Disease Free Survival

At the cut-off date (December 31, 2021), the median follow-up duration was 52 months (range, 7–116 months). 24 patients (34.6%) in the preoperative CRT group and 28 patients (55.8%) in the postoperative CRT group had died.

Univariate analysis showed that there was a significant difference in overall survival and disease free survival between the two groups (Table 3). The 5-year overall survival rates was 65.3% for the preoperative CRT group and 34.7% for the postoperative CRT group ($p = 0.010$). The 5-year disease free survival rates was 85.3% for the preoperative CRT group and 53.5% for the postoperative CRT group ($p = 0.007$).

Kaplan Meier survival curves (Figures 2a an 2b) showed that shorter survival was observed in the postoperative CRT group ($p < 0.0001$) and the preoperative CRT group were associated with a low recurrence rate and therefore had longer disease free survival ($p < 0.0001$). The Overall Survival at five years was significantly different between preoperative and postoperative arm (65.4 % vs. 44.2 %; $p = 0.010$). The disease Free Survival at five years was significantly higher in the preoperative CRT arm than in the postoperative CRT arm (85.3% vs. 53.5%; $p = 0.007$).

In this study, observed that preoperative CRT, pathologic tumour stage, pathologic node stage, histologic grade were statistically significant prognostic factors for both overall survival and disease free survival (Table 3).

Adverse Events Profile

Among the preoperative CRT group, 17 patients (21%) experienced adverse events of any grade (Table 4). The acute events related to CRT reported in 12 patients (14.8%) and chronic events in 5 patients (6.2%).

In the postoperative CRT group, 20 patients (46.5%) experienced adverse events of any grade including acute events in 15 patients (34.9%) and chronic events in 5 patients (11. 6%). Postoperative CRT group had higher incidence of adverse events of any grade. There were no adverse events of ≥ grade 4 or death due to CRT complications in both groups.

Table 3. Prognostic factors for overall survival and Disease Free Survival

Variables		Number of patients (%)	Overall survival		Disease Free Survival	
			5-yr (%)	P value	5-yr (%)	P value
Age /years	< 50	39 (31.5)	56.4	0.801	66.7	0.86
	≥ 50	85 (68.5)	58.8		68.2	
Gender	Male	72 (58.1)	58.3	0.943	66.7	0.76
	Female	52 (41.9)	57.7		69.2	
Modality	Preoperative CRT	81 (65.3)	65.4	**0.010**	85.3	**0.007**
	Postoperative CRT	43 (34.7)	44.2		53.5	
Tumour site from anal verge/ cm	<5	32 (25.8)	59.4	0.861	62.5	0.46
	≥5	92 (74.2)	57.6		69.6	
CEA ng/ml	< 5	63 (50.8)	60.3	0.605	74.6	0.09
	≥ 5	61(49.2)	55.7		60.7	
Histological grade	Grade I	13 (10.5)	61.5		84.6	
	Grade II	81 (65.3)	63.2	0.174	70.4	0.02
	Grade III	30 (24.2)	43.3		53.3	
Pathologic tumour stage	T0	4 (3.2)	100	**0.013**	100	**0.001**
	Tis	3 (2.5)	78.1		100	
	T1	16 (12.9)	75.0		81.3	
	T2	32 (25.8)	56.3		76.0	
	T3	62 (50.0)	53.2		62.9	
	T4	7 (5.6)	28.6		42.9	
Pathologic nodal stage	No	58 (46.8)	62.2	**<0.0001**	89.7	**<0.0001**
	N1	42 (33.8)	42.9		61.9	
	N2	24 (19.4)	25.0		25.0	

CEA, carcinoembryonic antigen.

Table 4. Adverse events of preoperative chemoradiotherapy (CRT) and postoperative CRT

Adverse events	Preoperative CRT* (n=81) N (%)	Postoperative CRT* (n=43) N (%)
Acute	12 (14.8)	15 (34.9)
Fatigue	3 (3.7)	4 (9.3)
Proctitis	2 (2.5)	3 (7.0)
Dermatology events	1 (1.2)	2 (4.7)
Genitourinary events	3 (3.7)	3 (7.0)
Gastrointestinal events	3 (3.7)	3 (7.0)
Chronic	5 (6.2)	5 (11.6)

Fistula	2 (2,5)	2 (4.7)
Pelvic abscess	2 (2.5)	1 (2.3)
Bowel obstruction	1 (1,2)	2 (4.7)

**CRT: chemoradiotherapy*

Discussion

In this study, retrospectively we investigated the 5-year overall survival and 5-year disease free survival in preoperative CRT versus postoperative CRT for patients with locally advanced rectal cancer (stage II and III). Numerous studies have observed the efficacy of preoperative CRT for the patients with locally advanced rectal cancer [6, 8,10,11 and 20-23].

Our study observed that preoperative CRT group had significantly tumour regression. Tumour response after preoperative CRT is known as a significant prognostic factor in rectal cancer [10 and 11]. The rate of response (complete response vs. partial response vs. no response) significantly influences local relapses, disease free survival and a lower risk of distant metastases [24 and 25]. In the preoperative CRT group, 7 patients achieved pathologic complete response, 47 patients (81.0%) had negative lymph nodes and 33 patients (91.7%) presented with stage I, as observed in the current study.

Patients outcomes in term of overall survival rates upraised from 45% to70% from 1975 to 2012 of rectal cancer patients [6]. This improvement reflects advances in treatment such as preoperative CRT) [6]. A large study, 66,197 patients with locally advanced rectal cancer treated between 2004 and 2012, reported that the 5-year overall survival rates for patients treated with CRT followed by surgery, surgery and CRT and surgery alone were 72.4% 70.9% and 48.8%, respectively [7]. Roh et al. reported the 5-year overall survival was 74.5% vs. 65.6% ($p = 0.065$) and 5-year disease free survival was 64.7% vs. 53.4% ($p = 0.011$) in the preoperative and postoperative CRT group, respectively [8]. Other studies observed that there was no significant advantages to prognosis (overall survival and disease free survival).The 5-year overall survival rate was 76% vs. 74% ($p = 0.80$) and 5-year disease free survival rate was 68% vs. 65% ($p = 0.32$) in the preoperative and postoperative CRT group, respectively [12 and 15].

Through follow-up duration 52 months (range, 7–116 months), 24 patients (34.6%) in the preoperative CRT group and 28 patients (55.8%) in the postoperative CRT group had died. This study observed that there was significantly difference in overall survival and disease free survival between the two groups. The 5-year overall survival rate was 65.3% vs. 34.7% ($p = 0.010$) and 5-year disease free survival rates was 85.3% vs. 53.5% ($p = 0.007$) in the preoperative and postoperative CRT group, respectively. In agreements with other studies [7 and 8].

Although, preoperative CRT is effective in tumour regression of locally advanced rectal cancer and to improve local control and overall survival [7, 8,10-11]. However, it is associated with adverse events such as gastrointestinal [26, 27] and genitourinary [28 and 29] and surgical recovery delay [30].

In the current study we observed that postoperative CRT had higher ratio of adverse events of any grade than preoperative CRT group (46.5% vs. 21%) respectively, and there was no serious adverse events of ≥ grade 4 or death in both treatment groups. These finding in agreements with other studies [12 and 13].

There are some limitations to this study. Firstly, extracted data retrospectively from one center. Large material from multi centers may provide additional information to more clarification. Secondly, variables such as doctors choice for preoperative CRT or postoperative CRT, patients' treatment preferences and availability of treatment option may have inadvertently affected the allocation between two groups.

Conclusion

This present study observed that preoperative CRT group were associated with improved downing staging rate, with a long survival rates, with a low relapses rates and with a low risk of adverse events.

Authors' contributions

MR performed designed the present study, drafted manuscript, the writing and making data collection. AR and ME and analyzed data, review the manuscript, performed data interpretation and analysis. MR drafting and proof reading and discussions. EE make the statistical analysis and prepared the figures and Tables and reviewed the study, interpreted data and aided in drafting and proof reading of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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