Long-term follow-up of Locally Advanced Cancer Rectum Patients who Received Either Neoadjuvant Short Course Radiotherapy or Neoadjuvant Conventional Chemoradiation

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Abstract:

Background: Neoadjuvant radiotherapy with or without chemotherapy plays an important role in the treatment of LACR as it helps to decrease the size of the tumor and achieve sphincter preservation in addition to improving the local control. The optimal radiotherapy fractionation to be used is still debatable. Our study aimed to compare between preoperative short course RT and long course CRT regarding disease response and complications.

Methods: This retrospective study analyzed the data of all rectal cancer patients who received neoadjuvant treatment either short course radio therapy or long course chemoradiation during the period from January 2012 to December 2020, at radiation oncology department, south Egypt cancer Institute, Assiut University. The radiotherapy dose in Group (A) was 2500 cGY /5 fractions 500 cGY per fraction over 1 week, while in Group (B) was 4500 cGY /25 fractions (180 cGY per fraction,5 fractions per week, over 5 weeks) for standard risk PTV then 540 cGY /3 fractions boost for high risk PTV to complete 5040 cGY. patients in group (A) didn't received chemotherapy, while patients in group (B) received either capecitabine 825 mg/m^2 twice daily with radiotherapy or 5-Flourouracil prescribed at 225 mg/m^2 + leucovorin given I.V in the first 3 days and last 3 days of the radiotherapy course.

Results: Our study revised records of 66 rectal cancer patients with median follow-up period 45 months. Median age was 42 and 45 years for group (A) and group (B) respectively. The median overall survival was 45 and 49 months for group (A) and (B) respectively. The median disease free survival was 35 and 36 months for group (A) and (B) respectively. 36 cases (100.0%) in group (B) developed early toxicities versus 27 cases (90.0%) in group (A) (P=0.089). Diarrhea, mucous discharge, and fecal incontinence were more prevalent among patients in group (B) compared to group (A) (P=0.001, 0.001, and 0.017) respectively. Grade 3 toxicity was found only in group (B) patients, 3 cases (8.3 %) developed grade 3 diarrhea and 1 case (2.8%) developed grade 3 mucous discharge. three cases in group (A) (10.0%) versus only one case in group (B) (2.8%) developed late toxicity.

Conclusion: Neoadjuvant short course RT is comparable to and long course CRT for treatment of LACR.

Keywords: cancer rectum, short course RT, long course CRT.

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Introduction:

Colorectal cancer (CRC) is considered the third most common cancer diagnosed in both sexes following breast and lung cancers and the second most leading cancer of death worldwide following lung cancer. [1]

Neoadjuvant treatment for locally advanced cancer rectum has become the standard of care for many years. [2] Currently, there are many neoadjuvant treatment options that can be used for locally advanced cancer rectum treatment. The most common is conventional

radiotherapy concomitant with chemotherapy (long course radiotherapy (50.4 Gy in 28 fractions)) and hypofractionated radiotherapy (short course radiotherapy (25 Gy in 5 fractions)).[3]

Many studies when compared both treatment approaches had revealed that, there is no significant differences between them in terms of overall survival (OS), local control (LC), distant metastasis, relapse free survival (RFS), or late toxicities. [4-5]

Neoadjuvant Short course radiotherapy has better patient compliance and tolerance than neoadjuvant long course chemoradiation due to less toxicity. [6-7]

Patients and Methods:

This retrospective study analyzed the data of all patients diagnosed with rectal cancer and received neoadjuvant treatment either short course radio therapy or long course concurrent chemoradiation during the period from 2012 to 2020, at Radiation Oncology Department, South Egypt Cancer Institute, Assiut University.

Eligibility Criteria:

Our study included all patients with Pathologically proved rectal adenocarcinoma, aged between 18 to 70 years, WHO performance status 0-2, Stage T3, T4, N1, N2 M0, surgically resectable disease, who received neoadjuvant radiotherapy either short or long course.

Exclusion Criteria:

Patients with locally advanced inoperable disease, locally recurrent rectal cancer, metastatic disease, previous surgical treatment, radiotherapy or chemotherapy for rectal or other cancers, patients did not complete the entire treatment plan or patient files with incomplete data.

The following data was extracted from the records: general data about the population (age, gender), presenting symptoms of the disease, radiological examinations (magnetic resonance, multi-slice computed tomography), Proctoscopy or rectal ultrasonography, TNM stage, tumor grade, tumor location, treatment regimens (short or long course of radiotherapy), radiotherapy technique, interval and type of surgery, follow- up period.

All patients in both treatment groups were treated using C.T based, 3D treatment planning system. 15mv of x-ray energy was used to optimize the dose distribution in the tumor and to decrease the dose to critical organs.

The radiotherapy dose in Group (A) was 2500 cGY /5 fractions 500 cGY per fraction over 1 week, while in Group (B) was 4500 cGY /25 fractions (180 cGY per fraction,5 fractions per week, over 5 weeks) for standard risk PTV then 540 cGY /3 fractions boost for high risk PTV to complete 5040 cGY.

Regarding chemotherapy; patients in group (A) didn't received chemotherapy, while patients in group (B) received either capecitabine 825 mg/m^2 twice daily with radiotherapy or 5-Flourouracil prescribed at 225 mg/m^2 + leucovorin given I.V in the first 3 days and last 3 days of the radiotherapy course.

All patients in both treatment groups received adjuvant chemotherapy FOLFOX (5-Flourouracil, leucovorin, oxaliplatin) for 12 weeks.

Regarding surgery; it was performed within 7 days after radiotherapy ends for group (A) patients and 4-6 weeks after radiotherapy ends for group (B) patients.

Surgery was either anterior resection, abdominoperineal resection or resection with coloanal anastomosis.

Follow up:

follow up was done through reviewing the patients records and contacting patients via telephone. Follow up data concerning both early and late toxicities was collected for each treatment regimen. It was found that early toxicity was assessed daily in group (A) and weekly in group (B) during radiotherapy, then weekly for an additional 12 weeks for both groups. Late toxicity was assessed in the routine visit of patients after the first 3 months of radiotherapy ends.

Treatment response was assessed using pelviabdominal MRI or C.T at 3 months' intervals during the first year, every 6 months in the second year, and annually thereafter. According to RECIST criteria, [8] complete response (CR) is defined as disappearance of all masses, lesions or any pathological L.N, must have reduction in short axis to <10mm. Partial response (PR) is defined as at least 30% reduction in sum of diameters of the mass or target lesion. Progressive Disease (PD) is defined as at least a 20% increase in the sum of diameters of lesions (the sum must also demonstrate an absolute increase of at least 5 mm), or appearance of new lesion or appearance of metastasis. Stable Disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Statistical methods:

All statistical calculations were done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22. Data were statistically described in terms of mean ± standard deviation (±SD), or median and range when not normally distributed, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using student t test. For comparing categorical data, Chi square (χ^2) test was performed, Fisher Exact test was used instead when the expected frequency was less than 5. OS and DFS were estimated using the Kaplan-Meier method. P-value is always 2 tailed set significant at 0.05 level.

Results:

Our retrospective study analyzed records of 66 patients (30 in group (A) and 36 in group (B)) with resectable locally advanced rectal adenocarcinoma in the period from January 2012 up to the end of

December 2020 in radiation oncology department, South Egypt Cancer Institute, Assiut university.

The demographic data of both groups were summarized in Table (1). Median age was 42 years with age ranged from 20 to 66 years for group (A) and 45 years with age ranged from 22 to 68 years for group (B). Both groups were comparable regarding to age, sex and tumor grade with no statistically significant difference between them.

Also, the pathological characteristics were comparable between both studied groups with no statistically significant difference between them.

Regarding treatment response, results was comparable between both studied groups with no statistically significant difference (P=0.865), as shown in Table (2).

Regarding early toxicity, all patients in group (B) (100.0%) were found to develop early toxicities versus 27 cases (90.0%) in group (A) patients, with no statistically significant difference between them (P=0.089).

The development of diarrhea, mucous discharge, and fecal incontinence were more prevalent among patients in group (B) compared to group (A) patients (P=0.001, 0.001, and 0.017) respectively. Grade 3 toxicity wasn't found in group (A) patients. However, in group (B) patients grade 3 of diarrhea and mucous discharge was found in 3 cases (8.3 %) and 1 case (2.8%) respectively.

Meanwhile, the development of other early toxicities namely (dysuria, and perianal pain) were comparable between both studied groups with no statistically significant difference between them (P=0.166, 1) respectively, as shown in Table (3).

Regarding late toxicity, three cases in group (A) (10.0%) developed late toxicity versus only one case in group (B) (2.8%), with no statistically significant difference between them (P=0.323).

All late developed toxicities namely (diarrhea, mucous discharge, and dysuria) were comparable between both studied groups with no statistically significant difference between them (P=1, 0.203, 0.455) respectively. No more than grade 1 toxicity was observed in either group as shown in Table (4).

Regarding postoperative complications, Table (5) shows that, eight cases (26.7%) in group (A) were developed post-operative complications versus five cases (13.9%) in group (B), with no statistically significant difference between them (P=0.194).

All post-operative complications namely (intestinal obstruction, hemorrhage, constipation & paralytic ileus, fistula formation, and pain around colostomy) were comparable between both studied groups with no statistically significant difference between them (P=0.399, 1, 0.587, 0.587, and 0.203) respectively.

According to Kaplan-Meier analysis, the median follow-up duration of the 66 rectal cancer patients was 45 months (range, 42 to 49 months).

There was no significant difference in OS between both groups, the median overall survival was 45 months versus 49 months in group (A) and group (B) protocol respectively (P=0.190), Table (6) and Figure 1.

According to Kaplan-Meier analysis, the median disease free survival duration of the 66 rectal cancer patients was 35 months (range, 34 to 36 months).

There was no significant difference in DFS between CCRTH protocol and short course RTH protocol, the median disease free survival (months) was 36 months versus 35 months in both treatment protocol respectively (P=0.729), Table (7) and Figure 2.

Subgroup analysis in this study bases on sex, age group, T stage, nodal metastasis and distant metastasis showed no significant differences as regard overall survival and disease-free survival in both groups.

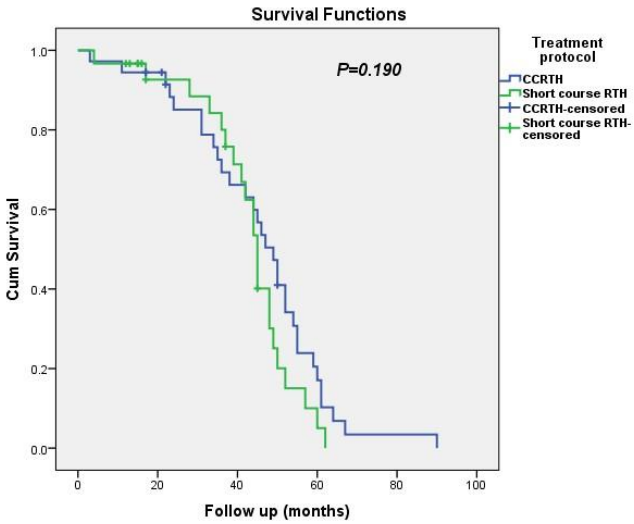

Fig. (1): Overall survival of the studied cohort according to the treatment protocol

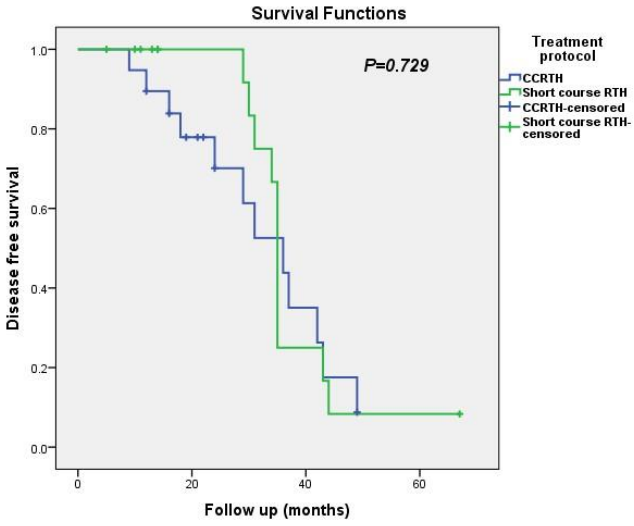

Fig. (2): Disease free survival of the studied cohort according to the treatment protocol

Table (1): Demographic data

Variable name	Short course RTH Group (A) (n=30)		CCRTH Group (B) (n=36)		P value
Age (years)					
• Mean ± SD	42.03 ± 12.24		45.03 ± 12.05		0.322
• Median (range)	42 (20 – 66)		45 (22 – 68)		
Gender, n (%)					
• Male	20	(66.7)	23	(63.9)	0.814
• Female	10	(33.3)	13	(36.1)	
Grade, n (%)					
• Grade 1	6	(20.0)	5	(13.9)	0.688
• Grade 2	17	(56.7)	24	(66.7)	
Grade 3	7	(23.3)	7	(19.4)	
TNM					
• T2	7	(23.3)	13	(36.1)	0.062
• T3	23	(76.7)	19	(52.8)	
• T4	0	(0.0)	4	(11.1)	
• N0	12	(40.0)	10	(27.8)	0.563
• N1	11	(36.7)	15	(41.7)	
• N2	7	(23.3)	11	(30.6)	
• M0	30	(100.0)	36	(100.0)	----

Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage). Significance defined by $p < 0.05$

Table (2): Treatment response

Variable name	Short course RTH Group (A) (n=30)	CCRTH Group (B) (n=36)	P value
Response after treatment			
• Regressive disease, n(%)	18 (60.0)	19 (52.8)	0.865
• Stationary disease, n(%)	10 (33.3)	14 (38.9)	
• Progressive disease, n(%)	2 (6.7)	3 (8.3)	

Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$

Table (3): Early toxicity

Variable name	Short course RTH Group (A) (n=30)		CCRTH Group (B) (n=36)		P value
Early toxicity, n(%)					0.089
• No	3	(0.0)	0	(10.0)	
• Yes	27	(100.0)	36	(90.0)	
Diarrhea, n(%)					**0.001***
• No	16	(11.1)	4	(53.3)	
• Grade 1	13	(69.4)	25	(43.3)	
• Grade 2	1	(11.1)	4	(3.3)	
• Grade 3	0	(8.3)	3	(0.0)	
Mucous discharge, n(%)					**0.001***
• No	7	(11.1)	4	(23.3)	
• Grade 1	23	(52.8)	19	(76.7)	
• Grade 2	0	(33.3)	12	(0.0)	
• Grade 3	0	(2.8)	1	(0.0)	
Fecal incontinence, n(%)					**0.017***
• No	29	(75.0)	27	(96.7)	
• Grade 1	1	(25.0)	9	(3.3)	
Dysuria, n(%)					0.166
• No	28	(80.6)	29	(93.3)	
• Grade 1	2	(19.4)	7	(6.7)	
Perianal pain, n(%)					1
• No	29	(94.4)	34	(96.7)	
• Grade 1	1	(5.6)	2	(3.3)	

Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$

TABLE (4): Late toxicity

Variable name	Short course RTH Group (A) (n=30)		CCRTH Group (B) (n=36)		P value
Late toxicity					0.323
• No	27	(90.0)	35	(97.2)	
• Yes	3	(10.0)	1	(2.8)	
Diarrhea					1
• No	30	(100.0)	35	(97.2)	
• Grade 1	0	(0.0)	1	(2.8)	
Mucous discharge					0.203
• No	28	(93.3)	36	(100.0)	
• Grade 1	2	(6.7)	0	(0.0)	
Dysuria					0.455
• No	29	(96.7)	36	(100.0)	
• Grade 1	1	(3.3)	0	(0.0)	

Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$

TABLE (5): Postoperative complications

Variable name	Short course RTH Group (A) (n=30)		CCRTH Group (B) (n=36)		P value
Post-operative complications					0.194
• No	22	(73.3)	31	(86.1)	
• Yes	8	(26.7)	5	(13.9)	
Intestinal obstruction					0.399
• No	26	(86.7)	34	(94.4)	
• Yes	4	(13.3)	2	(5.6)	
Hemorrhage					1
• No	29	(96.7)	35	(97.2)	
• Yes	1	(3.3)	1	(2.8)	
Constipation and paralytic ileus					0.587
• No	28	(93.3)	35	(97.2)	
• Yes	2	(6.7)	1	(2.8)	
Fistula formation					0.587
• No	28	(93.3)	35	(97.2)	
• Yes	2	(6.7)	1	92.8)	
Pain around colostomy					0.203
• No	28	(93.3)	36	1(00.0)	
• Yes	2	(6.7)	0	(0.0)	

Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$

Table (6): Overall Survival

Groups	Median				P value
	Estimate	Std. Error	95% Confidence Interval		
Group (A)	45.000	1.380	42.294	47.706	
Group (B)	49.000	2.802	43.508	54.492	0.190
Overall	45.000	1.786	41.500	48.500	

Table (7): Disease free survival

Groups	Median				P value
	Estimate	Std. Error	95% Confidence Interval		
Group (A)	35.000	0.300	34.412	35.588	
Group (B)	36.000	5.588	25.047	46.953	0.729
Overall	35.000	0.469	34.081	35.919	

Discussion:

Neoadjuvant concurrent chemoradiation followed by total mesorectal excision has become the standard therapy for locally advanced rectal cancer (LARC). Two different regimens of neoadjuvant radiation therapy are commonly used for LARC; short course radiotherapy (25 Gy in five fractions) and long course radiotherapy (45 to 50.4 Gy in 25 to 28 fractions). [9]

Bahadoer et al. conducted a study that enrolled 462 patients in short course group and 450 patients in CCRTH group. The authors stated that both groups had comparable baseline data. [10] Also, our study revealed that both groups either CCRTH or short course RTH group had insignificant differences as regard different baseline data and histopathological evaluation of the tumor.

The main finding in our study was that all patients who received CCRTH (100%) were developed early toxicities versus 27 cases (90%) who received short course RTH with no statistically significant difference. The development of diarrhea, mucous discharge, and fecal incontinence were more prevalent among patients who received CCRTH compared to patients who received short course RTH with no differences as regard other acute toxicities.

In agreement with our finding, Bahadoer et al. didn't show any significant differences as regard acute and late toxicities in both treatment groups. Grade 3 or more acute toxicity occurred in 219 (48%) of short course group, compared with 109 (25%) of CCRTH group. Diarrhea was the most common grade 3 or higher acute toxicity in both treatment groups. [10]

Chen et al. compared the efficacy of short course neoadjuvant RT with long course neoadjuvant CRT for rectal cancer treatment by meta-analysis and revealed that there were no significant differences regarding acute toxicities between both treatment groups. [11] Many other studies agreed such point. [12-14]

In the current study we found that the response status to both treatment regimens was comparable between both studied groups with no significant difference between them. The majority of both groups had regressive course. Similar findings were concluded in the Stockholm III trial where both groups had comparable response, the pathological complete response was reached in 29 (10·4%) of 285 patients in the short course regimen compared with only two (2·2%) of 94 patients after long course regimen. [15]

As regard postoperative complications, the current study found that five cases of those who received CCRTH (13.9%) developed post-operative complications versus eight cases (26.7%) of those who received short course RTH with no significant difference between them (P=0.194). In agreement with our study, Erlandsson et al. showed that both arms had insignificant differences as regard postoperative complications (50% vs. 39%; p= 0.07). [16] This was comparable with many previous studies. [10,12-14]

Also, in our study we found that there was no significant difference in OS between both groups, the median overall survival was 45 months versus 49 months for short course RTH protocol and CCRTH protocol respectively (P=0.190). Also, there was no significant difference in DFS between both groups, the median disease-free survival was 35 months versus 36 months for short course RTH protocol and CCRTH protocol respectively (P=0.72).

In line with our study, Chen et al. performed a meta-analysis to compare the prognostic performance of various short course and long course neoadjuvant RT. It stated that there was no significant difference between both treatment approaches in terms of 1–5 years' overall survival rates, complication rate, death rate, local recurrence rate, and the rate of distant metastasis. [11] This was comparable with many previous studies that concluded a comparable overall survival and disease free survival among both regimens. [6,10,12-14]

Meanwhile, Mohiuddin et al. revealed that long course neoadjuvant CRT has preferable survival outcome over short course neoadjuvant RT, particularly for distally located and advanced disease while the latter has clear advantages in patients' convenience and treatment cost. [17]

Also, Ngan compared the trials of either surgery alone, short course preoperative RT, preoperative CRT, or postoperative CRT, then recommended long course preoperative CRT for distally located tumors or bulky tumors and recommended short course preoperative RT when patients' convenience has to be considered at first. [18]

The main limitation of the current study included retrospective nature of the study that carried risk of bias. Another limitation was that short term of follow up where survival analysis may show significant differences with longer follow-up. Sample size of the study was relatively low to draw firm conclusion.

Conclusion:

Both neoadjuvant short course RT and long course CRT approaches are comparable in terms of overall survival, disease free survival, and complications when used for preoperative treatment of locally advanced cancer rectum. Multiple future randomized studies are warranted to draw firm conclusion.

List of abbreviations:

3D: Three dimensional
5-FU: 5-Fluorouracil cGY: Centi gray
CCRTH: Concurrent chemoradiotherapy
CR: Complete response
CRC: Colorectal cancer
CRT: Concurrent radiotherapy
CT: Computerized tomography
FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin
GY: Gray
LACR: Locally advanced cancer rectum
LC: Local control
MeV: Million electron volt
MRI: Magnetic resonance imaging
OS: Overall survival
PD: Progressive disease
PR: Partial response
PTV: Planning target volume
RFS: Relapse free survival
RT: Radiotherapy
SD: Stable disease
SPSS: Statistical package for the social science

Ethical statement:

The faculty of medicine ethical committee at Assiut University in Egypt has evaluated and approved the study. Each patient provided their informed permission before being enrolled in the study.

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