

## A PROSPECTIVE COMPARATIVE STUDY ON LOCALLY ADVANCED RECTAL CARCINOMA TREATED WITH PRE-OPERATIVE SHORT-COURSE RADIOTHERAPY VERSUS LONG-COURSE RADIOTHERAPY WITH CONCOMITANT CHEMOTHERAPY

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Received: 25 December 2021, Revised and Accepted: 05 February 2022

### ABSTRACT

**Objective:** In locally advanced non-metastatic rectal carcinoma, pre-operative radiotherapy is an acceptable alternative over post-operative radiation to improve locoregional control after radical surgery. There are two regimens of pre-operative radiotherapy – short-course radiotherapy (25 Gy/5 fractions/1 week) and long-course chemoradiotherapy (CRT) (50.4 Gy/28 fractions/5.5 weeks). Our study aimed to compare the pathological response, margin negative surgery rates, and treatment-related acute toxicities between these two approaches.

**Methods:** Patients with histologically proven locally advanced, non-metastatic rectal adenocarcinoma were randomized into study group and control group – the study group received short-course radiotherapy (25 Gy/5 fractions/1 week) followed by surgery after 7–10 days of completion of radiotherapy and the control group received long-course radiotherapy (50.4 Gy/28 fractions/5.5 weeks) with concurrent capecitabine followed by surgery after 4–6 weeks of completion of radiotherapy. Histopathology reports were studied in both groups for the determination of pathological response of tumor and surgical margin status. All patients received adjuvant chemotherapy for 6 months with oxaliplatin and capecitabine. For the assessment of treatment-related acute toxicities, patients were examined during the entire course of treatment.

**Results:** Overall pathological response (complete response+partial response) was 81.25% in the study arm and 86.66% in the control arm. Complete response rate was 15% in the study arm and 25% in the control arm. Margin negative surgery rates were higher in long-course CRT than short-course radiotherapy (90% vs. 82%), but it was statistically insignificant. Radiation-induced acute skin reactions (less than Grade 2) were significantly higher in long-course CRT arm (p=0.003).

**Conclusion:** There is no significant difference between pre-operative short-course radiotherapy and long-course concomitant CRT in terms of efficacy and acute toxicity profile. Thus, with our limited resources and huge patient load, short-course radiotherapy can be used as an acceptable alternative to long-course CRT.

**Keywords:** Locally advanced rectal carcinoma, Short-course radiotherapy, Long-course chemoradiotherapy.

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### INTRODUCTION

According to GLOBOCAN 2018 in India, around 24,251 new cases of rectal carcinoma occurred in 2018 contributing 2.6% of all cancer-related deaths [1,2]. Previously, surgery like abdominoperineal resection (APR) and low anterior resection (LAR) was considered the gold standard therapy, but there were high rates of local recurrence. Even with the advent of total mesorectal excision (TME), to reduce the chances of local recurrence [3-9]; there were still incidences of local recurrences opening up the potential role of adjuvant therapy in the form of radiotherapy, chemotherapy, or both to improve local control after TME [10].

Because of certain radiobiological disadvantages and higher incidence of bowel toxicity with post-operative radiation, neoadjuvant radiotherapy has come into the picture. Neoadjuvant treatment also has the advantages of tumor downstaging and subsequent higher potential of margin negative surgery, sphincter preservation, and reduced normal tissue toxicity [11,12].

There are two regimens for pre-operative radiotherapy – short-course radiotherapy (RT) (25 Gy/5 fractions/1 week) and long-course chemoradiotherapy (CRT) (50.4 Gy/28 fractions/5.5 weeks). Long-course radiotherapy provides time for adequate downstaging of tumor leading to better respectability, margin negative surgery, and higher pathological complete response (pCR) rates and better chances of sphincter sparing surgery. However, it has a long duration of treatment so requires prolonged hospital stay or repeated hospital visits, greater economic expenses, and more expenditure of resources.

In contrary, short-course RT is more compliant regimen due to shorter treatment time, allows early definitive surgery with comparable local control and overall survival with long-course therapy [13]. With our huge patient load and limited resources, we can use short-course radiotherapy without compromising the oncological outcome. Hence, we did this study comparing the short-course radiotherapy and long-course CRT in terms of treatment efficacy and acute toxicity profile for the management of locally advanced rectal carcinoma.

### METHODS

It was a double-arm, single-institutional prospective, comparative study in patients with locally advanced (T1-2N+, T3-4, N any, and M0) adenocarcinoma of rectum aged between 20 and 70 years having adequate hepatic, renal, hematological parameters, and an ECOG score of 0–2. Patients with recurrent rectal carcinoma, previous history of any other malignancy, or chemotherapy or radiotherapy were excluded from the study.

#### Study technique

Patients were randomized into two groups:

#### *In control arm (long-course chemoradiotherapy)*

Patients received pre-operative long-course radiotherapy at a dose of 50.4 Gy in 28 fractions in 5.5 weeks with tablet capecitabine 825 mg/m<sup>2</sup> orally twice daily throughout the entire course of radiation. Four to six

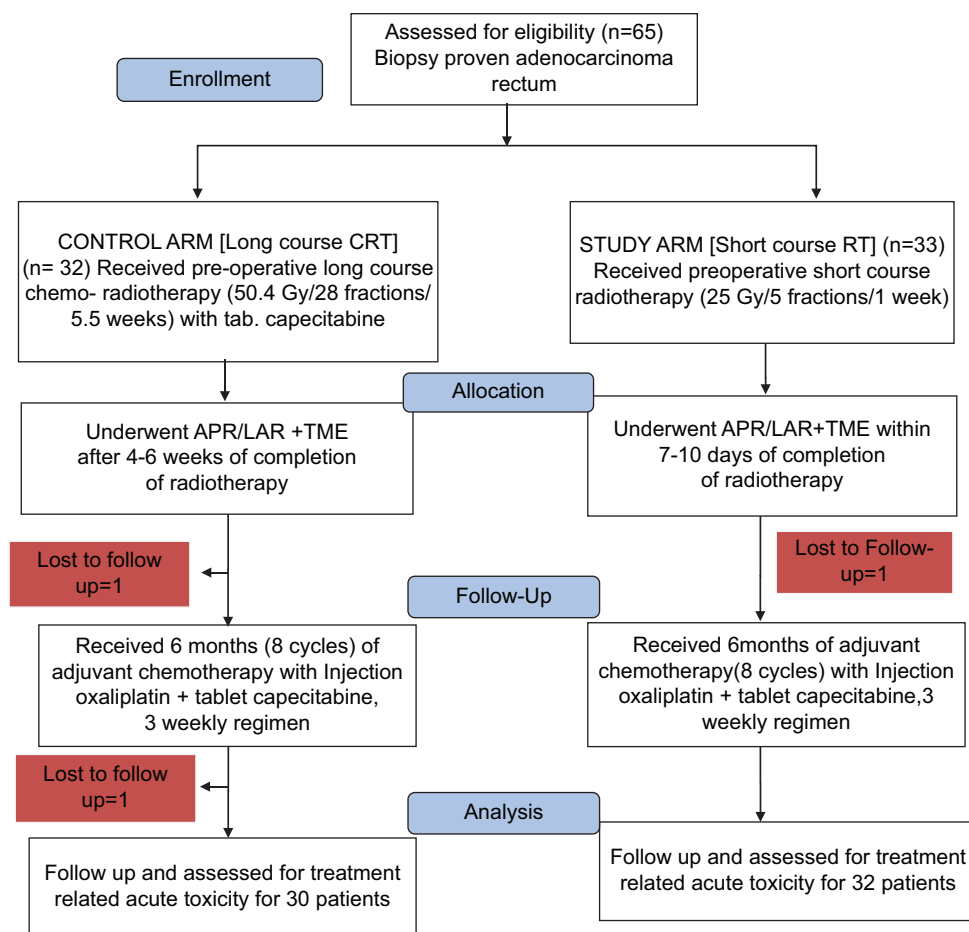


Fig. 1: Consort diagram

Table 1: Distribution of baseline characteristics between two arms of the study

Characteristics	Arm of the study		Total sample size	p
	Control arm (n=30)	Study arm (n=32)		
Mean age of patients (years), range	47.00 (28-62)	49.4062 (27-64)	-	-
Gender				
Male	25	26	62	0.54
Female	5	6		
Total	30	32		
Stage				
IIA	3	5	62	0.702
IIB	4	7		
IIC	2	4		
IIIA	13	9		
IIIB	6	6		
IIIC	2	1		
Total	30	32		
Performance status (ECOG score)				
0	2	3	62	0.917
1	15	15		
2	13	14		
Total	30	32		

Table 2: Margin status assessment between two arms

Arm of study	Margin status		Total	p
	Negative	Positive		
Study	26	6	32	0.27
Control	27	3	30	
Total (n)	53	9	62	

weeks after completion of chemoradiation, patients underwent radical surgery (APR/LAR+TME).

*In study arm (short-course radiotherapy)*

Patients received pre-operative radiotherapy at a dose of 25 Gy in five fractions in 1 week. Then, 7-10 days after completion of radiation patients underwent radical surgery (APR/LAR+TME).

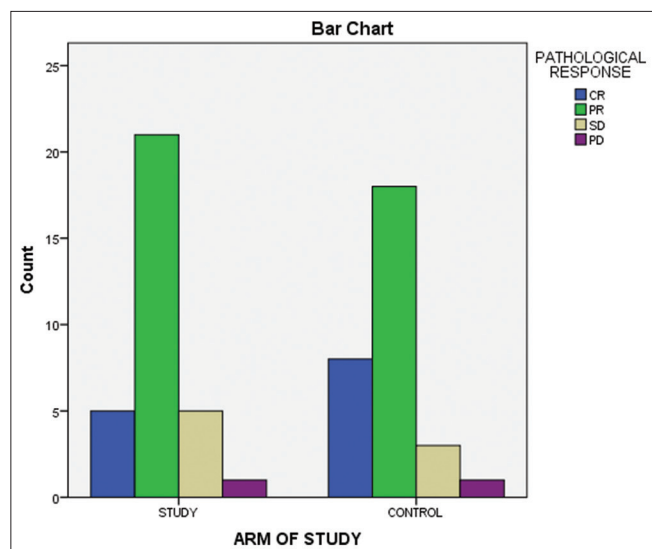


Fig. 2: Pathological response in surgical specimen after pre-operative therapy

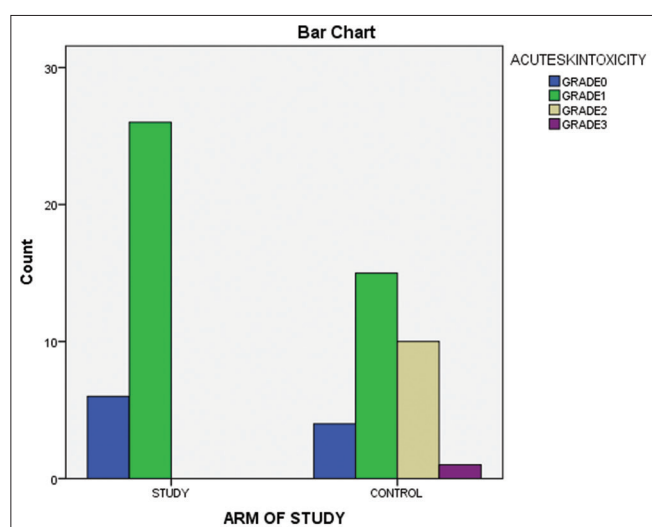


Fig. 3: Acute skin reactions between two arms of the study

After surgery, all patients in both the groups received adjuvant chemotherapy for 6 months with injection oxaliplatin (130 mg/m<sup>2</sup>) day 1 and tablet capecitabine (1000 mg/m<sup>2</sup>) per-oral bid day 1-14 every 3 weeks.

#### Radiotherapy technique

Radiotherapy delivered by means of conventional 2D planning using "Theratron 780E" telecobalt machine with conventional four-field box technique consisting of:

1. Anteroposterior/posteroanterior pelvic portal and
2. Right and left lateral opposed portals.

Final histopathology report after radical surgery was studied for the determination of pathological response and assessment of margin negativity. Circumferential resection margin of more than 1 mm was taken as adequate. Response assessment was done using RECIST1.1. All patients were followed up for treatment-related acute toxicity during the entire course of treatment and then at every month for the first 3 months and then 3 monthly for 6 months with at least 6 months of follow-up for each patient after completion of treatment. Follow-up included proper history of complaints, clinical examination, CBC, LFT, KFT parameters, and other necessary investigations as indicated including imaging.

Treatment-related toxicities were assessed as per toxicity assessment tools – CTCAE (Common Terminology Criteria for Adverse Events scale v5.0) and with radiation therapy oncology group scoring.

There is no source of financial grant or other funding.

#### Statistical analysis

Data were analyzed and compared according to appropriate statistical tests using SPSS v.20 software and Microsoft Word-Excel. Data were summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Unpaired proportions were compared by Chi-square test or Fisher's exact test, as appropriate. Any  $p < 0.05$  was considered statistically significant.

#### RESULTS

A total of 62 patients (32 study arm and 30 control arm) were analyzed in the two arms of the study (Fig. 1). Patients of both the arms were comparable in terms of mean age, gender, stage at presentation, and initial performance status (Table 1).

Majority of the patients in both arms had Stage IIIA disease (control arm 13 patients, 43.33% vs. study arm nine patients, 28.12%,  $p = 0.702$ ). Stage IIB was the next more common in the study arm and IIIB in the control arm.

Overall pathological response (CR+PR) seen in 81.25% of the study and 86.66% of the control arm population. About 25% of patients showed CR in long-course CRT arm than 15% in short-course RT, but the difference is statistically insignificant,  $p$ -value (0.71) (Fig. 2).

Margin negative surgery rates were 90% in long-course CRT arm and 80% in short-course radiotherapy arm. Around 18% of short-course RT patients had margin positive surgery in comparison to 10% in the control arm. However, these differences were statistically insignificant ( $p = 0.71$ ) (Table 2).

Radiation-induced acute skin reactions were significantly high in long-course chemoradiation (CRT) than short-course RT arm. About 33.3% of patients of long-course CRT arm suffered from Grade 2 skin reactions whereas there was no such reaction in short-course RT arm. This difference was statistically significant ( $p = 0.003$ ) (Fig. 3).

No statistically significant differences were found in terms of other toxicities such as bowel toxicity, bladder toxicity, and hematological toxicity between the two arms of the study. However, numerically higher grade of these toxicities was observed in long-course CRT arm whereas lower grade toxicities were common in short-course radiotherapy arm.

#### DISCUSSION

Pre-operative radiotherapy has an established role in the treatment of locally advanced rectal carcinoma. There are two approaches for this pre-operative therapy – first, long-course CRT and second, short-course RT alone.

The mean age of patients in the study arm was 49.4 years for the study arm and 47 years for the control arm. Age impacts colorectal cancer incidence greater than any other demographic factor, with the median age of diagnosis in the seventh decade. However, incidence rates have increased dramatically between ages 40 and 50 years over the past two decades [14]. This trend of disease in younger patients is also reflected in our study.

About 81% of patients were male in the study arm and 83% of patients of the control arm were male; echoing the fact that in almost all countries, age-standardized incidence rates for colorectal carcinoma are less for women than men [15].

Evaluation of histopathology reports was done after radical surgery (APR/LAR±TME) to assess the effect of pre-operative radiotherapy on

the tumor. Twenty-five (25%) of patients who received long-course CRT achieved complete pathological response as compared to 15% who received short-course RT. Overall response rate (partial + complete response) is also high in long-course CRT arm than short-course RT arm. Rate of margin negative surgery is also higher in long-course CRT arm than short-course RT. However, these differences were not statistically significant.

The reason behind this high rate of pCR and margin negative surgery in long-course CRT arm is the treatment time. Long-course radiotherapy had a long overall treatment time and surgery in this arm was done after 4–6 weeks interval compared to only 7–10 days in short-course arm. This prolonged treatment time allows for tumor downstaging leading to higher rates of margin negative surgery in long-course chemo-RT arm. Tumor regression also leads to higher pCR rate in operative specimen.

Polish rectal cancer study group in their Phase III trial among 312 patients also showed the similar results as of our study. Chemo-RT had higher pCR rates and lower rates of radial margin involvement. However, overall survival, local control of disease, and late toxicities were not different between long-course CRT and short-course RT arm [13].

Australian intergroup trial compared short-course RT and long-course CRT between 326 patients. At a follow up of 3 years, there was no difference in local control between the two arms. There was also no difference in 5-year OS and late toxicity [16].

Recently published Stockholm III trial randomized patients into three arms-(1) short course RT followed by surgery within one week (2) Short course RT followed by surgery after 4-8 weeks and (3) Long course CRT followed by surgery after 4-8 weeks. Here also, both short-course and long-course treatments were equivalent in terms of overall survival and local control. However, patients who received short-course RT followed by delayed surgery had lower ypT stage, higher rates of pCR (11.8% vs. 1.7%), and higher likelihood of tumor regression (10.1% vs. 1.7%) reflecting the fact that short-course RT with delay may be an alternative to conventional short-course RT followed by immediate surgery [17,18].

Analysis of toxicity profile between both the arms of study revealed statistically significant higher radiation-induced acute skin reaction in the control arm (long-course CRT). There were 33.3% of patients with Grade 2 skin reaction in the control arm where there was no Grade 2 toxicity in the study group ( $p=0.003$ ).

Bowel, bladder, and hematological toxicity were numerically higher in long-course CRT arm than short-course RT arm, though it was not statistically significant.

Long-course CRT arm was associated with higher radiation-induced skin reaction as it was given over a duration of 5.5 weeks which was sufficient for the expression of skin reactions. However, short-course RT got completed within 5 days followed by surgery within 7–10 days, which is very much less time than that required for the expression of acute reaction. Second, acute reactions are mainly dependent on total dose and overall treatment time; both of which were higher in the control arm causing severe skin reactions and other acute toxicities. Finally, the control arm involved concurrent chemotherapy potentiating the effects of RT and its toxicity. Chemotherapy also contributed separately to bowel, bladder, and hematological toxicity. Thus, higher grade of these toxicities was seen in our study in the control arm.

Polish rectal cancer group showed same result in their Phase III trial with higher rate of early toxicity in the chemo-RT group (18.2% vs. 3.2%) than short-course RT arm [13].

However, there are certain limitations in this study. At first, the sample size was small. Second, it was a single-institutional study; hence, results

derived cannot be extrapolated on entire population. Entire study duration was almost 18 months including patient accrual, intervention, and assessment. Hence, the late toxicity profile, disease-free survival/ progression-free survival, overall survival, late toxicities, and quality of life after treatment cannot be assessed appropriately.

## CONCLUSION

It can be said that in terms of efficacy and acute toxicity profile, there is no significant difference between pre-operative short-course radiotherapy and long-course concomitant CRT in the treatment of locally advanced rectal carcinoma. Thus, short-course radiotherapy can be used as an alternative to long-course CRT in our daily practice to treat a large number of patients with our limited resources. Especially in this era of COVID-19 pandemic, this type of short-course treatment protocols is very much useful in tumor control, while lessening the chances of acquiring the infection by shortening the hospital visits by the patients. However, further studies with larger sample size and longer duration of follow-up are necessary for defining an ideal treatment approach with special emphasis on long-term disease control and treatment-related late toxicities.

## ACKNOWLEDGMENT

Nothing to declare.

## AUTHORS' CONTRIBUTIONS

Linkon Biswas was involved in all part of the research specially concept, design, content, and preparation of first draft of the manuscript. Avik Maji and Shyam Sharma did data acquisition, data analysis, manuscript editing, and literature search. Prof. Srikrishna Mandal did manuscript editing and literature search.

## CONFLICTS OF INTEREST

Nothing.

## FUNDING

Nothing.

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