A Prospective Observational Study Comparing Long-Course Conventional Neoadjuvant Chemoradiotherapy with Short-Course Radiotherapy Followed by Consolidation Chemotherapy with Delayed Surgery in Locally Advanced Rectal Cancer

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Abstract

Background  Polish and Australian randomized studies compared short-course radiotherapy (RT) with immediate surgery and long-course chemoradiotherapy (CRT) with delayed surgery. In these studies, similar long-term survival and local control have been reported for both these approaches, but pathological complete response (pCR) is not better with short-course RT. Moreover, studies have shown better tumor downstaging with delayed surgery. In this context, the use of short-course RT with delayed surgery may have some advantages and needs to be tested in clinical trials.

Patients and Methods  This was a two-arm, prospective, observational study, in which preoperative short-course RT followed by two cycles of chemotherapy was compared with the conventional neoadjuvant CRT in locally advanced rectal cancer. The primary end points were the rate of complete response and toxicity profile. The secondary end points were the rate of R0 resection, overall survival, and progression-free survival. The data obtained from the two arms were analyzed using Pearson’s chi-square test to determine the statistical significance between the two treatment arms.

Results  The pCR rate was 6.7% in the study arm and 0 in the control arm ($p = 0.343$). The RO resection rates were 92.8 and 92.3% in the study and control arms, respectively. The rates of grade 3and 4 acute toxicity in the study and control arms were 14.2 and 61.5%, respectively ($p = 0.011$). The rates of grade 3 and 4 late toxicity in the study and control arms were 21.4 and 15.3%, respectively ($p = 0.686$).

Conclusions  The pCR rates and the late toxicities in both arms are comparable. The major advantages of the 5 × 5 Gy regimen with chemotherapy in a neoadjuvant setting are a significant reduction in acute toxicities and better patient compliance along with similar efficacy as that of the standard regimen.

Keywords  ► chemoradiotherapy  ► rectal neoplasm  ► short-course RT

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Introduction

The rectum is the most frequent site for intestinal cancer, with 40,000 cases annually, equally divided among both genders. Chemoradiotherapy (CRT) followed by surgery followed by adjuvant chemotherapy is the mainstay of treatment in stage II and III rectal cancer.

The incidence of local recurrence after conventional surgery, in which blunt dissection of the rectal fascia often fails to remove all the tissues that may bear tumor, is quite high (15–45%). In an attempt to improve local control and survival after conventional surgery, radiotherapy (RT) is given. The two broad approaches to preoperative pelvic RT for resectable rectal cancer are short-course RT and long-course CRT. In general, short-course RT delivers 25 Gy (5 Gy in five fractions) of radiation 1 week after surgery. Long-course CRT delivers 50.4 Gy (1.8 Gy in 28 fractions) of radiation concurrently with chemotherapy 4 to 8 weeks after surgery.

Polish and Australian randomized studies compared short-course RT with immediate surgery and long-course CRT with delayed surgery. In these studies, similar long-term survival and local control have been reported for both these approaches, but pathological complete response (pCR) is not better with short-course RT. A recent Stockholm III randomized trial compared preoperative short-course RT with immediate surgery and preoperative short-course RT with delayed surgery. An interim analysis reported better tumor downstaging with delayed surgery. Based on these findings, if surgery is delayed after short-course RT and chemotherapy is added before surgery, better pCR and tumor downstaging might be achieved. Another advantage of short-course schedule is that the rate of early toxicities is lower than that of conventional CRT and also it is more convenient for the patients.

Hence, the question is if the use of chemotherapy that is integrated closely with short-course RT followed by delayed surgery may increase the rate of pCR. In this context, the short-course RT may have some advantages and needs to be tested in clinical trials.

Patients and Methods

This was a hospital-based, comparative, two-arm, prospective, observational study conducted over a period of 12 months at the Department of Radiotherapy and Oncology, Regional Cancer Centre, Indira Gandhi Medical College & Hospital, Shimla, Himachal Pradesh, India, from July 2015 to June 2016. The study population consisted of cases of locally advanced rectal cancers who were selected on the basis of standard inclusion and exclusion criteria from the patients who presented at an outpatient department of Regional Cancer Centre, Shimla. A total of 28 patients were enrolled. Fifteen patients were in the study arm, i.e., short-course RT arm, and thirteen patients in the control or conventional RT arm. One patient in the study arm lost to follow-up after treatment. Thus, there were 27 evaluable patients. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all the study participants.

Inclusion criteria included patients aged >18 years and <75 years, having histologically proven rectal adenocarcinoma, cT3 or cT4 lesion, and Karnofsky performance status >70, and who were fit for major surgery.

Exclusion criteria included patients with prior treatment of rectal cancer, women who were pregnant, breastfeeding, or unwilling to use effective contraception, and patients with an associated medical condition or comorbid illness that impaired compliance.

Pretreatment Work-Up

Pretreatment workup included complete history and physical examination. Other investigations included complete hemogram, blood biochemistry, chest X-ray (posteroanterior), colonoscopy and biopsy, magnetic resonance imaging (MRI) of the abdomen and pelvis, and contrast-enhanced computed tomography (CECT) of the abdomen and pelvis if MRI is not performed. Pretreatment carcinoembryonic antigen testing was done for every patient.

Patients were assigned to the two treatment groups: the study and control group using stratified randomization based on gender, age, stage, and Karnofsky performance score (KPS). Patients in the control arm received tablet capecitabine at a dose of 1,650 mg/m² in two divided doses along with RT 5 days/week. Conventionally fractionated CRT with 45 Gy in 25 fractions to the whole pelvis was given. Patients in the study arm received 25 Gy in five fractions of 5 Gy followed by two cycles of capecitabine-and oxaliplatin-based chemotherapy. The chemotherapy was started 1 week after completion of short-course RT. The dose of capecitabine was 1,000 mg/m² given in two divided doses on days 1 to 14 and of oxaliplatin was 130 mg/m² on day 1. The second cycle was repeated after 21 days of the first cycle. Surgery was performed 4 to 6 weeks after completion of CRT. The surgery was performed as per the principles of total mesorectal excision in both arms. Adjuvant chemotherapy was routinely given in both arms 4 weeks after surgery.

End Points

The primary end points were the rate of complete response and toxicity profile. The secondary end points were the rate of R0 resection, overall survival (OS), and progression-free survival (PFS).

Response Assessment

Patients were reassessed clinically and radiologically after 6 to 8 weeks of completion of treatment. RECIST (Response Evaluation Criteria In Solid Tumours) 1.1 was used for response evaluation. In patients who underwent surgery, the response was assessed pathologically, and in those who could not undergo surgery due to any reason and had completed treatment, the response was assessed clinically and radiologically.

Assessment of Toxicities

Cutaneous toxicity, hematological toxicity, and gastrointestinal (GI) toxicity were categorized according to the Radiation
Thakur et al. (2020) investigated the efficacy of long-course conventional neoadjuvant CRT and short-course RT in locally advanced rectal cancer. At a median follow-up period of 22.6 months, seven (50%) patients in the study arm and eight (57.1%) patients in the control arm had a progressive disease. The pCR rate was 7.1% in the study arm and 0% in the control arm (p = 0.343). Also, 5 (35.7%) out of 14 evaluable patients in the study arm and 7 (53.8%) out of 13 evaluable patients in the control arm had a partial response (p = 0.274). Eight (57.1%) patients in the study arm and six (46.2%) patients in the control arm had a stable disease (p = 0.705). None of the patients in both arms had a progressive disease.

**Surgery**

Of the total of 28 patients, 12 patients did not undergo surgery. Three (23%) patients in the control arm and four (28.5%) patients in the study arm refused surgery. Two patients in each arm were found to be inoperable by the treating surgeon. Thus, a total of 16 (57.1%) patients out of 28 enrolled patients underwent surgery. Of the 16 patients who underwent surgery, 11 had sphincter-saving surgery. Six (40%) patients in the study arm and five (38.5%) patients in the control arm underwent low anterior resection (p = 0.934). Of the 11 patients who underwent low anterior resection, 3 had disease in the lower one-third, 3 had disease in the middle one-third, and 5 had disease in the upper one-third. All the patients who underwent abdominoperineal resection had disease in the lower one-third. Two patients in the control arm and three patients in the study arm had abdominoperineal resection (p = 0.502).

**Response**

The response could not be evaluated in one patient. One patient in the study arm lost to follow-up after treatment. Thus, there were 27 evaluable patients. Of the 27 evaluable patients, 16 patients underwent surgery and the response was assessed based on pathological findings, whereas 12 patients did not undergo surgery (due to various reasons described later) and the response was assessed radiologically with CECT/MRI of the abdomen and pelvis. The pCR rate was 7.1% in the study arm and 0% in the control arm (p = 0.343). Also, 5 (35.7%) out of 14 evaluable patients in the study arm and 7 (53.8%) out of 13 evaluable patients in the control arm had a partial response (p = 0.274). Eight (57.1%) patients in the study arm and six (46.2%) patients in the control arm had a stable disease (p = 0.705). None of the patients in both arms had a progressive disease.

**Statistical Analysis**

The data obtained from the two arms were analyzed using Pearson’s chi-square test to determine the statistical significance between the two treatment arms. Survival curves were constructed using the Kaplan–Meier method and were compared using the log-lank test.

**Results**

**Patient Characteristics**

A total of 28 patients were enrolled in the study: 15 in the study arm, that is, short-course RT/chemotherapy arm, and 13 in the control or conventional CRT arm. The patient characteristics (gender, age, smoking and drinking habits, and KPS) and disease characteristics (stage, grade, location, and type of growth) in the two arms were comparable.

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**Resection Margins**

Of 16 patients who underwent surgery, 1 patient in each arm had RI resection (p = 0.10). The rates of R0 resection were 92.8 and 92.3% in the study and control arms, respectively. None of the patients had R2 resection.

**Toxicity Assessment**

**Acute Toxicity**

The absence of hematological toxicity in 9 (64%) patients in the study arm was statistically significant (p = 0.001). One (7.6%) patient in the control arm had grade 3 hematological toxicity (p = 0.274). Also, 3 (21.4%) patients in the study arm and 12 (92.3%) patients in the control arm had grade 2 and 3 GI toxicity (p = 0.005). One (7.1%) patient in the study arm had grade 4 GI toxicity. The overall rate of GI toxicity was significantly lower in the study arm. The absence of skin toxicity in 11 (78.5%) patients in the study arm was statistically significant (p = 0.001). Grade 3 skin toxicity was seen in two (15.4%) patients in the control arm and none of the patients in the study arm (p = 0.116). None of the patients in either arm had grade 4 skin toxicity. The skin toxicities were significantly lower in the study arm. Hand–foot syndrome was seen in three (21.4%) patients in the study arm and three (23.1%) patients in the control arm (p = 0.843). Two (15.4%) patients in the control arm, and none of the patients in the study arm had grade 3 and 4 proctitis (p = 0.292).

The overall rates of acute toxicity in the study arm and control arm were 14.2 and 61.5%, respectively (p = 0.011). The acute toxicity was significantly lower in the study arm.

**Late Toxicity**

Grade 3 small/large intestinal toxicity was seen in two (14.2%) patients in the short-course RT group and none of the patients in the control group. The differences were statistically nonsignificant (p = 0.258). Grade 3 skin and subcutaneous tissue toxicity was seen in one (7.6%) patient in the control arm and none of the patients in the study arm. The differences were nonsignificant. Grade 3 bladder toxicity was seen in one (7.1%) patient in the study arm and none of the patients in the control arm. None of the patients had grade 4 bladder toxicity. The overall rates of grade 3 and 4 late toxicity in the study and control arms were 21.4 and 15.3%, respectively (p = 0.686), and were not significantly different between the arms. None of the patients had toxicity-related death in any of the arms.

**Relapse**

The median follow-up period was of 22.6 months. Two (14.2%) patients in the study arm and one (7.6%) patient in the control arm had local relapse. The distant relapse was seen in one (7.1%) patient in the study arm and one (7.6%) patients in the control arm (p = 0.442).

**Overall Survival and Progression-Free Survival**

The median OS in the study and control arms was 18.7 and 25.9 months, respectively (p = 0.590). The median PFS in the study and control arms was 12.6 and 18.7 months, respectively (p = 0.492) (~ Figs. 1 and 2). At a median follow-up period of 22.6 months, seven (50%) patients in the study arm and four (30.7%) patients in the control arm had no evidence of disease, two (14.3%) patients in...
Fig. 1 Overall survival curve according to the treatment groups.

Fig. 2 Progression-free survival curve according to the treatment groups LC (Long-Course CRT arm), SC (Short-Course RT arm).
the study arm and two (15.4%) patients in the control arm had partial response, and two (14.2%) patients in the study arm and five (38.5%) patients in the control arm had stable disease ($p = 0.442$).

**Discussion**

Conventionally fractionated CRT with delayed surgery and short-course irradiation (25 Gy in five fractions) with immediate surgery are probably the most frequent regimens in the preoperative treatment of patients with resectable rectal cancer. Similar long-term survival, local control, and late morbidity have been reported for both these methods in the studies. The benefit of the short-course schedule is a lower rate of early toxicity than with standard CRT. Furthermore, short-course irradiation is economical and more convenient, especially in centers with large patient numbers. However, the matter of concern with high doses per fraction is late toxicity.

Some recent reports have shown promising results with a strategy of delivering short-course RT with delayed surgery.12-14 These nonrandomized studies support the view that short-course preoperative radiation results in downstaging if surgery is postponed. In addition, a Polish study in which patients were given short-course RT followed by three cycles of FOLFOX-4 showed an improved OS and toxicity profile.15

In a phase II multicenter study by the Dutch Colorectal Cancer Group16 in primary stage IV rectal cancer, an improvement in OS and toxicity profile was seen with short-course radiation followed by six cycles of capecitabine, oxaliplatin, and bevacizumab (restaging after two cycles), and resection of both primary tumor and metastasis.

As the evidence for tumor downstaging and improved survival with short-course RT has come to light in the studies and arguments for neoadjuvant chemotherapy, there is a rationale for applying this concept in patients with rectal cancer at high risk of local or systemic failure. Thus, with this background, this study was conducted to establish the efficacy of short-course preoperative RT followed by two cycles of consolidation chemotherapy in locally advanced rectal cancer.

In a phase III trial by the Polish Colorectal Study Group,15 outcomes and toxicity between short-course RT/chemotherapy and conventional CRT in 515 patients with stage cT3 or cT4 rectal cancer were compared. A short course of radiation (5 days) followed by three cycles of chemotherapy yielded comparable outcomes as those with conventional radiation with concurrent chemotherapy. Three-year disease-free survival and local failure rates were around 50 and 22% in each arm, respectively. OS also appeared to favor the short-course approach. In our study, comparable response rates were obtained as with long-course CRT. The median OS and PFS were comparable in both the treatment groups.

The secondary end point of our study was toxicity assessment. In a phase III study by the Polish Colorectal Study Group,15 the rates of acute events (73 vs. 81%) and toxicity-related deaths (1 vs. 3%) favored the experimental arm over the control arm. The rates of grade 3+ toxicities, however, were essentially the same (23 and 21%). Moreover, the need for RT dose reduction (0 vs. 8%; $p < 0.001$) or prolonged RT time (0 vs. 5%; $p < 0.001$) was reduced with short-course radiation as compared with the standard course. Postoperative complications (reoperation and surgery-related death) and late toxicity occurred with similar frequency in the two arms. In our study, the most commonly observed toxicity was GI toxicity. Overall, the acute toxicities were significantly lower in the short-course RT/chemotherapy arm. There was no toxicity-related death in any of the arms in our study. The late toxicities were comparable in both the treatment groups in our study.

R0 resection, the primary end point in the Polish Colorectal Study Group, was comparable between the experimental and control arms (77 vs. 71%; $p = 0.07$), a positive trend for short-course treatment. In our study, R0 resection rates were comparable in both the treatment arms.

In our study, the response rates and toxicities of short-course RT/chemotherapy and conventional CRT were compared in the neoadjuvant setting in locally advanced rectal cancer. The response rates and R0 resection rates were comparable in both the treatment arms. The rates of GI, skin, and hematological toxicities were significantly lower in the short-course RT/chemotherapy arm. Other toxicities between the two groups were found to be comparable, with a decreasing trend in the short-course/chemotherapy arm. This being a small study, no conclusive results can be drawn. However, short-course RT followed by chemotherapy may further be evaluated as an option of treatment in patients with locally advanced rectal cancer.

**Limitations**

The major limitation included the relatively small sample size, which could be attributed to the fact that the study was performed in a single institution, which happens to be located in a hill state of Northern India, and in a time-bound manner as the enrollment was conducted for a period of 1 year only. Moreover, many of the patients did not qualify for the specified inclusion criteria. It is important to note that similar studies need to be conducted in future with multi-institutional collaboration to offset the issues concerning the limited sample size.

**Conclusions**

Based on our results, we strongly believe that short-course RT followed by chemotherapy in the neoadjuvant setting can be used as an effective alternative to conventional CRT in locally advanced rectal cancer as it has similar efficacy with the added advantage of improved toxicity profile compared with standard CRT. Moreover, short-course RT regimen followed by chemotherapy is more convenient for the patients and the treating physicians. However, as the sample size was very small, larger studies with longer follow-up need to be conducted to validate the results.
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Conflict of Interest
There are no conflicts of interest.

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References
1. Harnsberger JR, Vernava VM III, Longo WE. Radical abdominopelvic lymphadenectomy: historic perspective and current role in the surgical management of rectal cancer. Dis Colon Rectum 1994;37(1):73–87
2. Phillips RK, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following 'curative' surgery for large bowel cancer: I. The overall picture. Br J Surg 1984;71(1):12–16
3. Kapiteijn E, Marijnen CA, Colenbrander AC, et al. Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: a population-based study in the west Netherlands. Eur J Surg Oncol 1998;24(6):528–535
4. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24(28):4620–4625
5. Bosset JF, Calais G, Daban A, et al; EORTC Radiotherapy Group. Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance. Report of the 22921 randomised trial conducted by the EORTC Radiotherapy Group. Eur J Cancer 2004;40(2):219–224
6. Marijnen CA, Peeters KC, Putter H. Long term results, toxicity and quality of life in the TME trial. Radiother Oncol 2004;73(Suppl 1):S127–S128
7. Birgisson H, Pålman L, Gunnarsson U, Glimelius B; Swedish Rectal Cancer Trial Group. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. J Clin Oncol 2005;23(34):8697–8705
8. Initial report from a Swedish multicentre study examining the role of preoperative irradiation in the treatment of patients with resectable rectal carcinoma. Swedish Rectal Cancer Trial. Br J Surg 1993;80(10):1333–1336
9. Marijnen CA, Kapiteijn E, van de Velde CJ, et al; Cooperative Investigators of the Dutch Colorectal Cancer Group. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2002;20(3):817–825
10. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004;72(1):15–24
11. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345(9):638–646
12. Radu C, Berglund A, Pålman L, Glimelius B. Short-course preoperative radiotherapy with delayed surgery in rectal cancer - a retrospective study. Radiother Oncol 2008;87(3):343–349
13. Hatfield P, Hingorani M, Radhakrishna G, et al. Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. Radiother Oncol 2009;92(2):210–214
14. Pettersson D, Holm T, Iversen H, Blomqvist L, Glimelius B, Martling A. Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 2012;99(4):577–583
15. Bujko K, Wyrwicz L, Rutkowski A, et al; Polish Colorectal Study Group. Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol 2016;27(5):834–842
16. Van Dijk TH, Havenga K, Beukema J, et al. Short-course radiation therapy, neoadjuvant bevacizumab, capecitabine and oxaliplatin, and radical resection of primary tumor and metastases in primary stage IV rectal cancer: a phase II multicenter study of the Dutch Colorectal Cancer Group. J Clin Oncol 2010;28:295