Panacea Journal of Medical Sciences 2020;10(3):235–239

Content available at: https://www.ipinnovative.com/open-access-journals

Panacea Journal of Medical Sciences

Journal homepage: www.ipinnovative.com

Original Research Article

Hypofractionated short-course preoperative conformal radiotherapy versus long course conventional preoperative chemoradiotherapy in the management of locally advanced rectal cancer – Prospective randomized comparative study

Nithya Nutan B[1,*], Tapas Maji[2], Biplab Misra[2], Mallika A[3], Debarshi Lahiri[4], Sanjoy Roy[4]

[1]*Dept. of Radiation Oncologist, Ashwin Hospital, Coimbatore, Tamil Nadu, India*
[2]*Dept. of Radiotherapy, Chittaranjan National Cancer Institute, Kolkata, West Bengal, India*
[3]*Dept. of Radiotherapy, Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India*
[4]*Dept. of Radiation Oncology/Radiotherapy, Chittaranjan National Cancer Institute, Kolkata, West Bengal, India*

ARTICLE INFO

Article history:
Received 10-08-2020
Accepted 01-10-2020
Available online 29-12-2020

Keywords:
Chemoradiotherapy
Preoperative treatment
Rectal cancer

ABSTRACT

Introduction: Colorectal cancer (CRC) is the primary health problem worldwide. Besides survival, a significant problem in locally advanced rectal cancer is recurrence. Adding radiotherapy to surgery has been shown conclusively to improve local control for rectal cancer.
Aim: To compare hypo fractionated short-course preoperative conformal radiotherapy versus long-course conventional preoperative chemoradiotherapy in the management of locally advanced rectal cancer.
Materials and Methods: This prospective comparative study was conducted in 44 patients who grouped into ARM A (short course RT) for 22 patients and ARM B (long course Chemoradiotherapy) for 22 patients. Treatment protocol and follow up protocol was followed and the results were statistically analyzed and discussed.
Results: Out of 44 patients, 22 patients had short-course radiotherapy (ARM A) and 22 patients had long course radio-chemotherapy (ARM B). In ARM A, 7 patients in stage T3NOMO, 2 patients in stage T3N1MO,9 patients in stage T4N0M0, 4 patients in stageT4N1M0,4patients had an interruption, 18 patients had no interruption, mean duration of diseases free survival is 354.59 ±125.86 days, 18 patients had a partial response, and 4 patients had stable diseases. In ARM B,5 patients in stage T3NOMO, 5 patients in stage T3N1MO, 7 patients in stages T4N0M0, 5 patients in stage T4N1M0, 14 patients had an interruption, 8 patients had no interruption, mean duration of diseases free survival is 414.27±119.97 days, 19 patients had a partial response and 3 patients had stable diseases.
Conclusion: Short-course neo-adjuvant radiotherapy using IMRT showed similar response rates and diseases free survival but less acute toxicity and short hospital stay when compared to the conventional long-course chemoradiotherapy.

1. Introduction

Colorectal cancer (CRC) is a leading health problem worldwide. Colorectal cancer is the second most common cancer in women and the third most common cancer in men worldwide.[1] In India, colon cancer ranks 9^{th} and rectal cancer 10^{th} among the most common cancers in men. Among women, rectal cancer does not feature in the top 10 cancers, whereas colon cancer was ranking 9^{th}.[2] In 2013, the highest adjusted incidence rate (AAR) in men for CRCs was recorded in Thiruvananthapuram (4.1), Bengaluru (3.9) and Mumbai (3.7). Among women, the highest AAR was recorded in Nagaland (5.2) then by Aizawl (4.5).[2]

* *Corresponding author*.
E-mail address: doc.nithin0507@gmail.com (N. Nutan B).

https://doi.org/10.18231/j.pjms.2020.049

The specialized cancer wing of the world health organization (WHO), International Agency for Research on Cancer (IARC), released the latest data on cancer incidence, mortality, prevalence worldwide in December 2013.[3] Their online database GLOBOCAN 2012 revealed the most recent estimates of incidence and prevalence rates of different cancers. Colorectal cancer has become the third most common cancer worldwide preceded by only lung and breast cancer, with nearly 14 million new cases of all sex in the year 2012.

Worldwide nearly 8,00,000 new cases of colorectal cancer are believed to occur each year, which accounts for approximately 10% of all incident cancer. Mortality from colorectal cancer is estimated at nearly 4,50,000 per year.[4]

Geographic variation in colorectal cancer incidence implies the critical role of the environmental factors. A 30-40 fold difference is seen between the highest and the lowest incidence areas. Generally speaking, colorectal cancer incidence and mortality rates are most significant in developed western contries.[4–7] It ranges from more than 40 per 1,00,000 people in the united states, Australia, New Zealand and western Europe to less than 5 per 1,00,000 in Africa and some parts of Asia.[8]

The pattern of variation in incidence was much different for women and men. The incidence of men was highest in towns with better socio-economic status, but among women, the trend was reversed. This suggests the dominant etiological influences causing colorectal cancer differ in both sexes.[9]

In the year 1989, the truncated incidence rates for rectal cancer at the Delhi Cancer Registry were 5.4 in males and 4.0 in females.[10]

Mortality rates for colorectal cancer worldwide are approximately half of its incidence. Nearly about 5,30,000 deaths were recorded in the year 2012, and its contribution was up to 8 % of all cancer-related deaths. Colorectal cancer has become the second leading cause of death among other cancers, both in men and women, in the united states. The mortality rate is unaffected even with the present advancement in treatment but may be influenced by modern diagnostic techniques and screening programs.[11]

2. Aim

Our study aims to compare hypo fractionated short-course preoperative conformal radiotherapy versus long-course conventional preoperative chemoradiotherapy in the management of locally advanced rectal cancer.

3. Materials and Methods

This prospective randomized comparative single institutional study was conducted in Chittaranjan National Cancer Institute, Kolkata from August 2014 to April 2016 in the management of locally advanced rectal cancer.

3.1. Inclusion criteria

Histologically confirmed rectal adenocarcinoma, with lower borders within 12 cm of the anal verge, ultrasound or MRI staged T2N+, T3N0, T3N+, T4aN0/+ diseases, ECOG score 0-2, haemoglobin$\geq$10gm/dl, neutrophil count $\geq$ 4,000/cmm, platelet count $\geq$ 1,00,000/cmm, bilirubin and ALT $\leq$ 1.5 times the upper limit of normal, serum creatinine $\leq$ 1.5 times the upper limit of normal, no evidence of metastasis.

3.2. Exclusion criteria

Rectal cancer other than adenocarcinoma, locally advanced inoperable cancer such as T4, presence of metastasis, any previous chemotherapy or radiotherapy, concurrent uncontrolled medical conditions, pregnancy or feeding, evidence of hereditary colorectal cancer and familial adenomatous polyposis, clinically significant cardiac diseases, myocardial infarction

After getting written consent form, eligible patients were randomly assigned to receive either short-course radiotherapy in ARM A and conventional long-course Chemoradiotherapy in ARM B.

ARM A (short-course radiotherapy) comprised of patients getting radiotherapy alone with a total of 25Gy in 5 fractions administered in 1 week, followed by surgery 7 days later. Capecitabine 1250mg/m^2 twice daily in days 1-14, every three weeks, to a total of six months of preoperative therapy period was administered.

ARM B (long-course chemoradiotherapy) comprised patients receiving a total of 50.4Gy in 28 fractions over 5 weeks and Capecitabine 825mg/m^2 twice daily for 5 days a week for the duration of radiation. Surgery following 4-6 weeks of chemoradiotherapy was planned. Six-month preoperative courses of the same chemotherapy as for short course radiotherapy patients were commenced 4-6 weeks post-surgery.

The radiotherapy equipment used in this study is a dual-energy (6MV and 15MV) linear accelerator. Radiotherapy related toxicities were assessed every weekly during radiotherapy and followed up at 3 months, 6 months, 1 year, 2 years and 5 years after treatment by standard form.

4. Results

Out of 44 patients, 22 patients had short-course radiotherapy and 22 patients had long course radiotherapy. The mean age of patients with short-course radiotherapy was 44.27$\pm$13.47 years and in patients with long course radiotherapy was 46.72$\pm$11.97 years. (Table 1)

Out of 22 patients who had short-course radiotherapy, 15 patients were males, 7 patients were females and out of 22 patients had long course radiotherapy, 16 patients were males, 6 patients were females. (Table 2)

Table 1: Age distribution in two groups of patients.

Age (Years)	Short Course RT	Long Course RT
20-29	4	3
30-39	3	2
40-49	7	7
50-59	6	7
60-69	2	3

Table 2: Gender in two groups of patients.

Gender	Short Course RT	Long Course RT
Males	15	16
Females	7	6

Out of 44 patients, 22 patients had short-course radiotherapy and 22 patients had long course radiotherapy. Out of 22 patients had short-course radiotherapy, 7 patients were in stage T3NOMO, 2 patients were in stage T3N1MO, 9 patients were in stage T4N0M0, 4 patients were in stage T4N1M0 and out of 22 patients had long course radiotherapy, 5 patients were in stage T3NOMO, 5 patients were in stage T3N1MO, 7 patients were in stage T4N0M0, 5 patients were in stage T4N1M0. (p value=0.57) (Table 3)

Table 3: Stages of diseases in two groups of patients.

Stage	Short Course RT	Long Course RT
T3N0M0	7	5
T3N1M0	2	5
T4N0M0	9	7
T4N1M0	4	5

Table 4: Degree of Differentiation in two groups of patients.

Degree of Differentiation	Short Course RT	Long Course RT
MDC	12	13
PDC	4	4
WDC	6	5

The degree of differentiation of the patients of the two groups was more or less equally distributed. (p value=0.93) (Table 4)

There was no statistical difference in mean distance of anal verge of the patients in short-course radiotherapy 5.50±1.69cmand long-course radiotherapy 5.52±1.76cm. (P-value =0.97)

In both groups, 90.9% of the patients underwent colostomy.

Out of 22 patients who had short-course radiotherapy, 4 patients had an interruption in treatment, 18 patients had no interruption in treatment and out of 22 patients had long course radiotherapy, 14 patients had an interruption in treatment, 8 patients had no interruption in treatment. (Table 5)

Table 5: Interruption in treatment in two groups of patients.

Interruption in Treatment	Short Course RT	Long Course RT
Yes	4	14
No	18	8

The proportion of patients with anaemia, leucopenia, diarrhoea, skin reaction, dysuria was significantly higher in long course radiotherapy, in short-course radiotherapy. (Table 6)

Table 6: Reactions in two groups of patients.

Reaction	Short Course RT	Long Course RT	P-value
Anemia	5	14	0.015
Leucopenia	3	16	<0.0001
Diarrhoea	3	16	<0.0001
Skin reaction	3	14	0.002
Dysuria	2	13	0.002

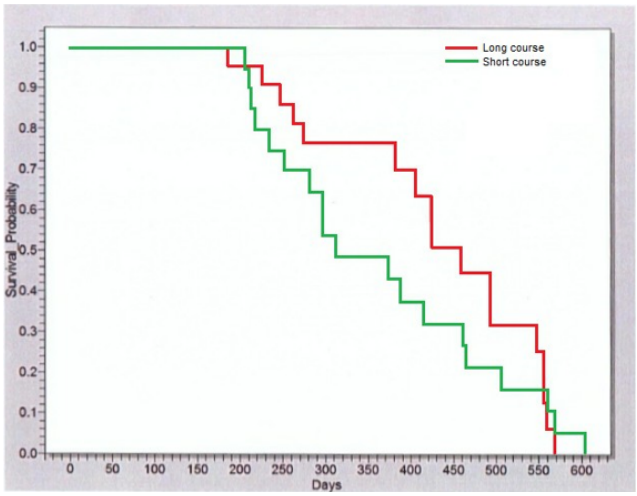

Fig. 1: Survival analysis

Survival of long course radiotherapy was better than that of short-course radiotherapy, the log-rank test showed that there was no statistically significant difference between them (Log-rank test =0.32, p=0.57). (Figure 1)

Out of 22 patients who had short-course radiotherapy, the mean duration of diseases free survival is 354.59 ±125.86 days and out of 22 patients had long course radiotherapy, the mean duration of diseases free survival is 414.27 ±119.97 days. (Table 7)

Out of 22 patients who had short-course radiotherapy, 18 patients had a partial response and 4 patients had stable diseases and out of 22 patients had long course radiotherapy, 19 patients had a partial response and 3 patients had stable diseases. (Table 8)

Table 7: Duration of diseases free survival in two groups of patients.

Duration of diseases free survival (Days)	Short Course RT	Long Course RT
Mean	354.59 ±125.86	414.27 ±119.97

Table 8: Response to treatment in two groups of patients.

Response to Treatment	Short Course RT	Long Course RT
Partial response	18	19
Stable diseases	4	3

5. Discussion

Surgery has been the principal curative modality for a long time in the treatment of rectal cancers. In many cases of locally advanced (TMN stages 2 and 3) carcinoma of rectum primary curative surgery is not possible because of extensive local involvement by the tumour. They were termed as primarily unresectable tumours.

The standard approach to these unresectable rectal cancer patients has been neoadjuvant therapy (radiotherapy ± chemotherapy) followed by surgery. This is because that surgery alone would leave residual tumour in the pelvis. The main goals of preoperative RT are to convert an unresectable tumour to a resectable tumour and to decrease the incidence of local failure rates by facilitating resection with no residual diseases (R0). The treatment of full-dose preoperative RT converts 48% to 64% of patients to a resectable state.[12–14]

The main issue concerning the use of combined modality therapy is whether the addition of chemotherapy to radiotherapy in the neo-adjuvant setting increases the resectability rate, response rate and local control rates and whether there is any improvement in terms of diseases-free survival and overall survival. Also, the addition of chemotherapy is associated with a greater increase in acute toxicities.

In the present study, the effect of standard neoadjuvant chemoradiotherapy has been compared with the result of a short course preoperative RT without chemotherapy. In this study, 44 patients of carcinoma rectum staged T2N+ or T3N0/N+, or T4aN0/N+ were accrued.

Among those patients, 22 of them were randomized to study arm receiving pre-op short-course RT, whereas the remaining 22 patients were randomized to control arm to receive long course pre-op concurrent chemoradiotherapy. All the patients were assessed for response before surgery by clinical imaging and local examination by colonoscopy. All the 44 patients completed the full course of treatment and were eligible for statistical analysis.

In both arms, 44 patients received a full course of treatment. Among the 22 patients in the short course RT group, 18 patients (81.8%) and in long course CCRT group 19 patients (86.4 %) achieved partial response in terms of local diseases and nodal disease. The remaining 4 patients in the study arm and 3 patients in the control arm had stable diseases. The outcome was 81.8% and 86.4% in the study arm and control arm, respectively, which is comparable and satisfactory.

Till the last follow up of the patients, 18 patients in the study arm and 19 patients in the control arm were diseases free, after full treatment. The mean diseases free survival of patients in short course RT arm was 354.59 days and in long course chemoradiotherapy arm it was 414.27 days, whereas median diseases free survival in short course RT arm was 322.50 days and in long course chemoradiotherapy arm it was 423.50 days. The mean and median duration of diseases free survival was higher in the long course chemoradiotherapy group than that of short-course radiotherapy group, but it was not significant (p=0.06).

In the short course RT arm 4 patients and 3 patients in long course chemoradiotherapy arm, presented with recurrent diseases within the irradiated field or distant

Metastasis during the subsequent course of follow up.

After post-treatment assessment, the resectability rate for the CCRT arm was 80%. These results are more or less comparable to those observed by Minsky BD et al. (89%), and Leong T et al. (91%).[15,16] This variability of results may be attributed to various factors. Firstly, because these data are historical and from different institutions, there were non- uniformity regarding patient selection, clinical staging, and also difference in the preoperative treatment. 5-FU was used as chemotherapy in all these trails.

All the acute toxicities, in the short course radiotherapy arm, were within manageable limits and overall, the whole course of treatment was tolerated well by most of the patients. Overall acute toxicities mostly observed were in the range of 0-3. There were no grade 4 toxicities.

In the long course chemoradiotherapy arm, acute toxicities were much higher during the end of the full course of treatment. There was an interruption during the course of treatment, but the treatment could be completed. Grade 3 anemia was noted in 3 patients (13.6%) and grade 3 diarrhea was noted in 2 patients (9.1%), whereas grade 2 anemia in 1 patient (4.5 %) and leucopenia in 1 patient (4.5%) diarrhea in 6 patients (27.3%) skin reaction in 3 patients (13.6%), dysuria in 1 patient (4.5%) was noted.

Haematological toxicities, followed by diarrhoea and skin reaction, were the most common cause of treatment interruption. Interruption of treatment due to acute toxicities in long course arm was 63.6% when compared to only 18.2% in study arm. The reason was obviously due to the long course of treatment as well due to concurrent chemotherapy which might aggravate the acute toxicities. Till the last date of follow up, the late toxicities were those

of small and large intestine followed by urinary bladder.

In the short course RT arm 3 patients (13.6%) with grade 1 bladder toxicities, 4 patients (18.2%) with grade I gastrointestinal toxicities and 2 patients (9.1%) with grade 1 skin toxicities were noted, whereas in long course arm 2 patients (9.1%) with grade 1 bladder, 2 patients (9.1%) with grade 1 gastrointestinal toxicities, 1 patient (4.5%) with grade 1 skin toxicities were noted.

There were no significant differences in late toxicities during the follow-up period. Longer follows up period is required to fully assess the late effects. Because of the short follow-up duration and in the absence of a clear cut definition and description of late toxicities in other studies, the comparison of them with the present study was difficult.

6. Conclusion

In locally advanced rectal cancer neoadjuvant treatment in the form of chemoradiation has become the standard of care. It has also been shown to improve both local control and survival of the patients. Long course chemotherapy delays the surgery and subject the patients to acute toxicities, causing prolonged hospitalization and greater inconvenience. In the present study, the short-course neo-adjuvant radiotherapy using IMRT showed similar response rates and diseases free survival but less acute toxicity and short hospital stay when compared to the conventional long course chemoradiotherapy.

7. Source of Funding

No financial support was received for the work within this manuscript.

8. Conflict of Interest

The authors declare they have no conflict of interest.

References

1. GLOBOCAN 2012. 2014;Available from: http://www.globocan.Iarc.Fr/pages/fact_sheets_cancer.Aspx?Cancer=colorectal.
2. National cancer Registry Programme, India council of Medical Research: three years report of population based cancer registries; 2009-2011.
3. World Health Organization. Cancer incidence in five continents. Lyon: the world health organization and the international agency for research on cancer; 2002.
4. Parkin DM, Pisani P, Ferlay J. Global cancer statistics. *CA: A Cancer J Clin*. 1999;49(1):33–64. doi:10.3322/canjclin.49.1.33.
5. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. *CA: A Cancer J Clin*. 1998;48(1):6–29. doi:10.3322/canjclin.48.1.6.
6. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer*. 1975;15(4):617–31. doi:10.1002/ijc.2910150411.
7. Henderson MM. International differences in diet and cancer incidence. *J Natl Cancer Inst Monogr*. 1992;(12):59–63.
8. O'connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Rates of colon and rectal cancers are increasing in young adults. *Am Surg*;69(10):866–72.
9. Barker DJ, Godfrey KM. Geographical variations in the incidence of colorectal cancer in Britain. *Br J Cancer*. 1984;50(5):693–8. doi:10.1038/bjc.1984.238.
10. National Cancer Registry Programme. Biennials report 1988-1989. An epidemiology study. Indian council of medical research, Delhi; 1992. p. 136–7.
11. Davies RJ, Miller R, Coleman N. Colorectal cancer screening: prospects for molecular stool analysis. *Nat Rev Cancer*. 2005;5(3):199–209. doi:10.1038/nrc1569.
12. Dosoretz DE, Gunderson LL, Hedberg S, Hoskins B, Blitzer PH, Shipley W, et al. preoperative irradiation for unresectable rectal and recto sigmoid carcinomas. *Cancer*. 19831;52(5):814–8.
13. Emami B, Pilepich M, Willett C, Munzenrider JE, Miller HH. Effect of preoperative irradiation on resectability of colorectal carcinomas. *Int J Radiat Oncol Biol Phys*. 1982;8(8):1295–9. doi:10.1016/0360-3016(82)90578-8.
14. Mendenhall WM, Million RR, Bland KI, Pfaff WW, Copeland EM. Initially Unresectable Rectal Adenocarcinoma Treated with Preoperative Irradiation and Surgery. *Ann Surg*. 1987;205(1):41–4. doi:10.1097/00000658-198701000-00007.
15. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) Phase III Trial of Combined-Modality Therapy for Esophageal Cancer: High-Dose Versus Standard-Dose Radiation Therapy. *J Clin Oncol* . 2002;20(5):1167–74. doi:10.1200/jco.2002.20.5.1167.
16. Leong T, Smithers BM, Michael M. TOPGEAR: a randomized phase III trial of perioperative ECF chemotherapy versus preoperative chemoradiation plus perioperative ECF chemotherapy for resectable gastric cancer (an international, intergroup trial of the AGITG/TROG/EORTC/NCIC CTG). *BMC Cancer*. 2015;15:532.

Author biography

Nithya Nutan B, Consultant

Tapas Maji, HOD

Biplab Misra, Senior Resident

Mallika A, Senior Consultant

Debarshi Lahiri, Specialist

Sanjoy Roy, Specialist Radiation Oncologist

Cite this article: Nutan B N, Maji T, Misra B, Mallika A, Lahiri D, Roy S. Hypofractionated short-course preoperative conformal radiotherapy versus long course conventional preoperative chemoradiotherapy in the management of locally advanced rectal cancer – Prospective randomized comparative study. *Panacea J Med Sci* 2020;10(3):235-239.