*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*
*e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 3 Ver.17 March. (2018), PP 04-12*
*www.iosrjournals.org*

# Long-Course Conventional Neoadjuvant Chemoradiotherapy Versus Short Course(5*5 Gy) Radiotherapy Followed By Consolidation Chemotherapy With Delayed Surgery In Locally Advanced Carcinoma Rectum: Results Of A Prospective Randomized Study

Niketa Thakur, R.K. Seam, M.K. Gupta, M. Gupta, V. Fotedar, S.Vats, Sakshi Rana,
*(Department Of Radiotherapy And Oncology, Regional Cancer Center, IGMC, Shimla , India).*
*Corresponding Author: Niketa Thakur*

***Abstract:*** ***Background:*** *Chemoradiotherapy followed by surgery followed by adjuvant chemotherapy is the mainstay of treatment in stage II and III rectal cancer.There are two approaches to pelvic RT for resectable rectal cancer: short-course radiation and long course chemoradiotherapy(CRT).Polish and Australian randomized studies compared short-course radiation and immediate surgery with long-course CRT and 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.****So the idea is to combine the benefits of delayed surgery for improved tumor downstaging with short course RT by adding two cycles of chemotherapy between short course RT and surgery to improve pCR rates.****In this context the use of short-course radiotherapy may have some advantages and needs to be tested in clinical trials.*

***Aim:*** *To compare the tumour response clinically, radiologically and histopathologically*
*To compare the toxicities between the two arms*

***Materials and Methods:*** *This prospective randomized study was a two arm study in which short course radiotherapy followed by two cycles of chemotherapy was compared with conventional neoadjuvant chemoradiotherapy in rectal cancer.Patients assigned to study group(short course RT) were given 25 Gy (5 Gy/fraction) in 5 days.Following a gap of 1 week after RT, patients were given two cycles of Capecitabine and Oxaliplatin (CAPOX) based chemotherapy.Patients assigned to control group(conventional CRT) were given radiation of 50.4 Gy in 28 fractions along with tablet Capecitabine on RT days.Patients were assessed for surgery*
*after 4-6 weeks of completion of chemoradiation.Overall treatment time to surgery was similar in both the arms i.e.*
*10-12 weeks.*

***Results:*** *Of the 28 entered patients, 27 were eligible for analysis; 14 in study arm and 13 in control arm.The pCR rate was 6.7% in study arm while it was 0 in control arm(p=0.343). 33.3% patients in study arm and 53.8% patients in control arm had partial response(p=0.274). 53.3% patients in study arm and 46.2% patients in control arm had stable disease(p=0.705).None of the patients in both the arms had progressive disease.Acute toxicities were lower in study arm.The absence of hematological toxicity in 60% patients in study arm was statistically significant (p=.001).20% patients in study arm and 92.3% patients in control arm had grade 2-3 toxicity (p=0.005).The absence of skin toxicity in 73.3% patients in study arm was statistically significant(p=.001).Grade 3 toxicity was seen in 15.4% patients in control arm and no patient in study arm(p=0.116).*

***Conclusions:*** *pCR rates in the two arms are comparable.But the major advantage for the 5*5 Gy regimen with chemotherapy in neo-adjuvant setting is the improved toxicity profile compared with conventional CRT with significant reduction in acute toxicities in short course RT arm.*

***Keywords:*** *Short-course RT, rectal neoplasm, chemoradiotherapy*

---

Date of Submission: 16-03-2018 Date of acceptance: 31-03-2018

---

## I. Introduction

The rectum is the most frequent site for intestinal cancer, with 40,000 cases annually, equally divided by gender. Chemoradiotherapy 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 tissue that may bear tumor, is quite high (15 to 45 percent)[1,2,3]. In an attempt to improve local control and survival after conventional surgery, radiotherapy is given. The two broad approaches to preoperative pelvic radiation therapy for resectable rectal cancer are: short-course radiation and long course chemoradiotherapy. In general, short-course radiation delivers 25 Gy (5 Gy in five fractions) of radiation followed by surgery 1 week later. Long-course chemoradiotherapy delivers 50.4 Gy (1.8 Gy in 28 fractions) of radiation concurrently with chemotherapy, followed by surgery 4 to 8 weeks later.

The studies showed that the addition of fluoropyrimidine to neoadjuvant radiotherapy compared with radiotherapy alone significantly reduced the risk of local recurrence.[4]The addition of 5-Fluorouracil and Leucovorin/Capecitabine to conventionally fractionated chemoradiation is considered as standard in resectable rectal cancer.

The benefit of the short-course schedule is a lower rate of early toxicity than with chemoradiation[4-10,11] and also it is more convenient.

Polish and Australian randomized studies compared short-course radiation and immediate surgery with long-course CRT and delayed surgery.In these studies studies similar long-term survival and local control have been reported for both these approaches but pathological complete response is not better with short course RT. To improve the pathological complete response if we add chemotherapy to short course RT, better outcome can be achieved. **So the question is if the use of neoadjuvant chemotherapy that is integrated closely with Short course radiotherapy followed by delayed surgery may increase the rate of pathological complete response.** In this context the short-course radiotherapy may have some advantages and needs to be tested in clinical trials.

Moreover a recent Stockholm III randomized trial compared preoperative short-course radiotherapy and immediate surgery with preoperative short-course radiotherapy and delayed surgery. An interim analysis reported better tumour downstaging with delayed surgery. Based on these findings, if surgery is delayed after short-course radiotherapy and chemotherapy is added prior to surgery, better pathological complete response and tumour downstaging might be achieved

So to test this hypothesis we conducted a prospective randomised trial comparing conventional chemoradiotherapy and delayed surgery with short course radiotherapy followed by two cycles of chemotherapy and delayed surgery.

## II. Aims And Objectives

To compare the response clinically, radiologically and histopathologically.

1. To compare the toxicity between the two arms under following heads:

- Gastrointestinal toxicity
- Hematological toxicity
- Skin toxicity
- Proctitis
- Hand foot syndrome

## III. Material And Methods

This study was two arm, two cohort study conducted in the Department of Radiotherapy, Regional Cancer Centre IGMC, Shimla from July 2015 to June 2016. **Patients with following characteristics were enrolled in this study:**

1. age>18 years,<75 years.
2. histologically proven rectal adenocarcinoma.
3. cT3 or lesion cT4
4.Written informed consent
5.Staging done within 5 weeks prior to randomization
6 .Karnofsky performance status > 70 and patient fit for major surgery
7.Adequate blood counts:

- White blood cell count ≥4.0 x 109/L
- Platelet count ≥100 x 109/L
- Clinically acceptable haemoglobin levels

10.Creatinine levels indicating renal clearance ≥ 50 ml/min

**Pre-treatment workup included:**

Complete history & physical examination . Other investigations included complete haemogram, blood biochemistry, chest X-ray (PA), colonoscopy and biopsy, histology and grade of the tumour, MRI of abdomen and pelvis, and CECT abdomen and pelvis if MRI not done. Pre-treatment CEA was done of each patient.

**Exclusion criteria**

- Tumour extension into sacrum above S3
- Tumour involving lumbosacral nerve roots
- Distant metastasis (M1)
- Recurrent rectal cancer
- FAP or HNPCC
- Active Crohn's disease or ulcerative colitis
- Concomitant malignancies
- DPD deficiency
- Inability to give informed consent
- Concurrent uncontrolled medical condition
- Any investigational treatment for rectal cancer within past month
- Pregnancy or breast feeding
- Known malabsorption syndromes
- Clinically significant cardiac disease
- Symptoms or history of peripheral neuropathy

**Randomization**

Patients were randomized to two groups: the study and control group using stratified randomization.

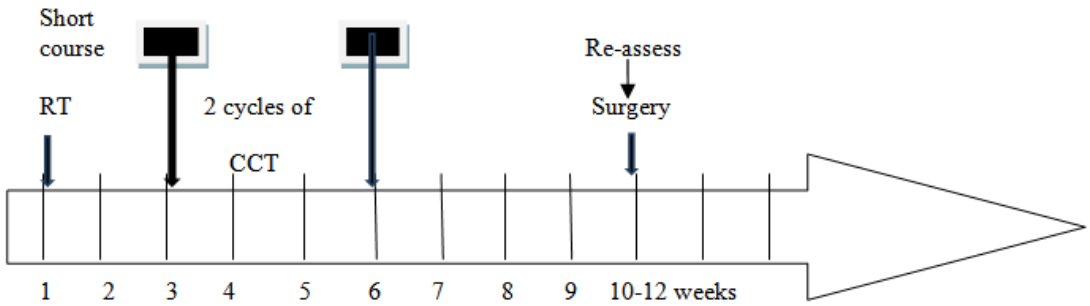
| **INTERVENTION** | **ARM A (STUDY)** | **ARM B (CONTROL)** |
|---|---|---|
| **RADIOTHERAPY** | 25 Gy in 5 fractions of 5 Gy followed by two cycles CAPOX based chemotherapy. | Conventionally fractionated chemoradiation with 45 Gy/25# to whole pelvis + 5.4 Gy/3# boost to GTV with margins |
| **CHEMOTHERAPY DRUG/DOSE** | Capecitabine1000mg/$m^2$ given in two divided doses and oxaliplatin 130mg/$m^2$. | Capecitabine 1650mg/$m^2$ given in two divided doses |
| **CHEMOTHERAPY DURATION** | 2 cyclesof chemotherapy.First cycle was given at an interval of 1 week after completion of RT<br>A cycle constituted -------- Tab Capecitabine 1000 mg/$m^2$in two divided doses D1-14<br>Inj oxaliplatin 130 mg/$m^2$-D1<br>2nd cycle repeated after 21 days of first cycle. | Days 1-5/week with radiation |

Surgery was done 4-6 weeks after completion of chemoradiotherapy. Neoadjuvant chemotherapy was started 1 week after completion of short course radiotherapy.

**Study design**

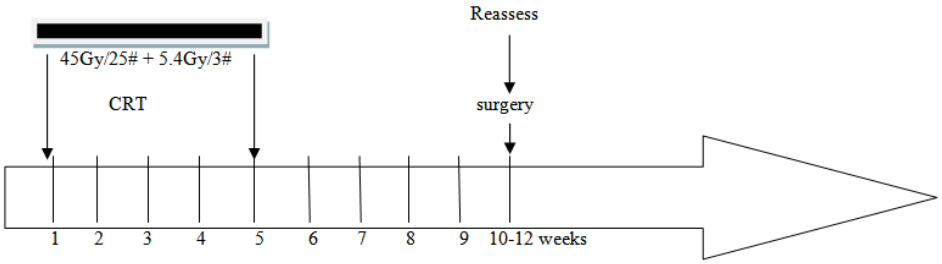
**Arm A (study arm)**

Short course radiotherapy was followed by two cycles of chemotherapy after 1 week of completion of RT.




**Arm B (control arm)**

**Tablet** Capecitabine 1650mg/$m^2$ in two divided doses, 5 days/week with radiation.




**Response assessment**

RECIST1.1 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(CECT/MRI abdomen –pelvis).

**Assessment of toxicities**

The expected toxicities of chemoradiation were compared.Skin reactions, hematological toxicity, gastrointestinal toxicity were categorized according to RTOG recommendations.Hand foot skin reactions and proctitis were graded as per the WHO grading system .

**Statistical analysis**

The data obtained from the two arms was analysed by Pearson Chi- square test to determine the statistical significance between the two treatment arms.

The statistical significance was defined as:

- ❖ $p > 0.05$ Non significant
- ❖ p 0.05 - 0.01 Significant
- ❖ $p < 0.01$ Highly significant

## IV. Results

**Patient Characteristics**

A total of 28 patients were enrolled in the study, 15 in the study arm i.e. Short course RT/chemotherapy arm and 13 in the control or conventional CRT arm. All patients were given radiotherapy as described along with the drug as per the arm under which they were treated. ***The patient and disease characteristics in the two arms were comparable (mentioned in table 1).***

**Table 1.**

| Patient Characteristics | Study arm (SC+Chemo) n=15 | Control arm (CRT) n=13 | Total n= 28 | p-value |
|---|---|---|---|---|
| **Age distribution** | | | | |
| Mean age(years) | 53.8 | 59.62 | | |
| 20-29 | 1(6.7%) | 0(0%) | 1(3.6%) | |
| 30-39 | 3(20%) | 1(7.7%) | 4(14.3) | 0.777 |
| 40-49 | 1(6.7%) | 2(15.4%) | 3(10.7) | |
| 50-59 | 2(13.3%) | 2(15.4%) | 4(14.3%) | |
| 60-69 | 6(40%) | 5(38.5%) | 11(39.3) | |
| 70-79 | 2(13.3%) | 3(13.3%) | 5(17.9) | |
| **Sex** | | | | |
| Male | 9(60%) | 8(61.5%) | 17(60.7%) | 0.934 |
| Female | 6(40%) | 5(38.5%) | 11(39.3%) | |
| **Smoking history** | | | | |
| Smoker | 6(40%) | 5(38.5%) | 11(39.3%) | 0.934 |
| Non-smoker | 9(60%) | 8(61.5%) | 17(60.7%) | |
| **Alohol consumption** | | | | |
| Chronic drinker | 2(13.3%) | 1(7.7%) | 3(10.7%) | |
| Occasional drinker | 3(20%) | 3(23.1%) | 6(21.4%) | 0.885 |
| non-drinker | 10(66.7%) | 9(67.2%) | 19(67.9%) | |
| **Diet** | | | | |
| Vegetarian | 4(26.7%) | 2(15.4%) | 6(21.4%) | 0.468 |
| Non-vegetarian | 11(73.3) | 11(84.6%) | 22(78.6%) | |
| **KPS** | | | | |
| 70 | 2(13.3%) | 0(0%) | 2(7.1%) | |
| 80 | 2(13.3%) | 3(23.1) | 5(17.9%) | 0.347 |
| 90 | 11(73.3%) | 10(76.9%) | 21(75%) | |
| | | | | |
| **Mean BSA** | 1.57 | 1.58 | | 0.332 |

| | | | | |
|---|---|---|---|---|
| **Histology** | | | | |
| Well. diff. adenoca. | 7(46.7%) | 5(38.5%) | 12(42.9%) | 0.911 |
| Mod. diff. adenoca. | 4(26.7%) | 4(30.8%) | 8(28.6%) | |
| Poorly diff. adenoca. | 2(13.3%) | 2(15.4%) | 4(14.3%) | |
| Mucin secreting ac | 2(13.3%) | 2(15.4%) | 4(14.3%) | |
| **Stage** | | | | |
| T2N+M0 | 3(20%) | 1(7.7%) | 4(14.3%) | |
| T3N0M0 | 0 | 323.1%) | 3(10.7%) | 0.213 |
| T3N+M0 | 7(46.7%) | 4(30.8%) | 11(39.3%) | |
| T4N0M0 | 0 | 1(7.7%) | 1(3.6%) | |
| T4N+M0 | 5(33.3%) | 4(30.8%) | 9(32.1%) | |
| **Tumour location** | | | | |
| Lower 1/3rd | 14(93.3%) | 9(69.2%) | 23(82.1%) | |
| Middle 1/3rd | 0 | 2(15.4%) | 2(7.1%) | 0.193 |
| Upper 1/3rd | 1(6.7%) | 2(15.4%) | 3(10.7%) | |
| | | | | |
| **Rectal wall invasion** | | | | 0.934 |
| Circumferential | 6(40%) | 5(38.5%) | 11(39.3%) | |
| **Type of growth** | | | | |
| Endophytic | 4(26.7%) | 2(15.4%) | 6(21.4%) | 0.692 |
| Exophytic | 3(20%) | 4(30.8%) | 7(25%) | |
| Ulcerative | 8(53.3%) | 7(53.8%) | 15(53.6%) | |
| **Involved lymph node** | | | | |
| Negative | 1(6.7%) | 1(7.7%) | 2(7.1%) | |
| Peri-rectal | 5(33.3%) | 6(46.2%) | 11(39.3%) | 0.561 |
| Presacral | 1(6.7%) | 3(23.1%) | 4(4.3%) | |
| Mesenteric | 5(33.3%) | 5(38.5%) | 10(35.7%) | |
| Iliac | 6(40%) | 215.4%) | 8(28.6%) | |
| | | | | |
| **Tumour size ($cm^2$)** | 5.8 | 7.09 | | 0.262 |

**Surgery**

Out of the total 28 patients, 12 patients did not undergo surgery, due to various reasons:

- 3(10%) patients in control arm and 4(25%) patients in study arm refused surgery.
- 2 patients in each arm were found inoperable by treating surgeon
- 1(10%) patient in the study arm refused further treatment

Thus, a total of 16 (57.1%) patients out of total 28 enrolled patients underwent surgery. Of the 16 patients who underwent surgery, 5 had sphincter saving surgery. 2 patients in study arm and 3 patients in control arm underwent sphincter saving surgery(p=0.502).Of the 5 patients who underwent low anterior resection 1 had disease in the lower 1/3, 1 had disease in the middle 1/3rd and 3 had disease in the upper 1/3rd. All the patients who underwent abdomino-perineal resection had disease in the lower 1/3rd.5 patients in the control arm and 6 patients in study arm had abdominoperineal resection patients (p=0.934).

**Resection margins**

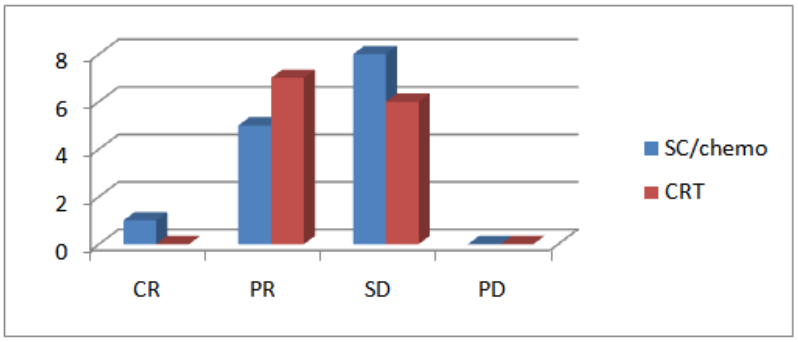
Out of the 16 patients who underwent surgery, 1 patient in each arm had R1 resection(p=1.000).7 patients in each arm had R0resection(p=1.000). None of the patient had R2 resection.

**Response**

Response could not be evaluated in 1 patient. 1 patient in study arm refused further treatment. Thus, there were 27 evaluable patients.Out of 27 evaluable patients, 16 patients underwent surgery and in them response was assessed histopathologically whereas 12 patients did not undergo surgery(due to various reasons described later) and in them response was assessed radiologically with CECT/MRI of abdomen-pelvis. The pCR rate was 6.7% in study arm while it was 0 in control arm(p=0.343).5 out of 14(33.3%) evaluable patients in study arm and 7 out of 13(53.8%) evaluable patients in control arm had partial response(p=0.274). 8 patients(53.3%) in study arm and 6 patients(46.2%) in control arm had stable disease(p=0.705).None of the patients in both the arms had progressive disease. The results of response are mentioned in table 2.

**Table 2.**

| Response | Study arm(n=14) | Control arm(n=13) | Total | p-value |
|---|---|---|---|---|
| CR | 1(6.7%) | 0 | 1(3.6%) | 0.343 |
| PR | 5(33.3%) | 7(53.8%) | 12(42.9%) | 0.274 |
| SD | 8(53.3%) | 6(46.2%) | 14(50.0%) | 0.705 |
| PD | 0 | 0 | 0 | |




**Toxicity assessment**

RTOG criteria were used for assessement of acute hematological, gastrointestinal, cutaneous toxicity and proctitits whereas WHO criteria were used for assessement of severity of hand foot syndrome. Toxicity results are mentioned in table 3.

**Hematological toxicity:** The absence of hematological toxicity in 9(60%) patients in study arm was statistically significant (p=.001).Grade 1 toxicity was present in 4(26.7%) patients in study arm and 10(76.9%) in control arm(p=.008).1 patient in control arm had grade 3 toxicity(p=0.274).

**Gastrointestinal toxicity**: 3(20%) patients in study arm had no GI toxicity. 3(20%) patients in study arm and 12(92.3%) patients in control arm had grade 2-3 toxicity. 1(6.7%) patient in study arm had grade 4 toxicity. The overall p-value of GI toxicity combined was 0.005.Thus, the overall gastrointestinal toxicity was found to be lower in the study arm.

**Skin toxicity**: The absence of skin toxicity in 11 patients (73.3%) in study arm was statistically significant. Grade 3 toxicity was seen in 2(15.4%) patients in control arm and no patient in patient in study arm(0.116).None of the patients in either arm had grade 4 toxicity.The overall p-value was 0.001.Therefore, statistically significant lower skin toxicities were seen in study arm.

**Hand foot syndrome**: Hand foot syndrome was seen in 3 (20.0%) of the patients in the study arm and in 3 patiens (23.1%) in control arm(p=0.843).

**Proctitis**: 2(15.4%) patients in control arm and none of the patients in study arm had grade 3-4 proctitis.The overall p-value was 0.292.

**Table 3.**

| Toxicities | Study arm (SC+CHEMO) N=15 | Control arm (CRT) N=13 | Total N=28 | p-value |
|---|---|---|---|---|
| **Haematological toxicity** | | | | |
| Grade 0 | 9(60%) | 0 | 9(32.1%) | |
| Grade 1 | 4(26.7%) | 10(76.9%) | 14(50%) | 0.006 |
| Grade 2 | 2(13.3%) | 2(15.4%) | 4(14.3%) | |
| Grade 3 | 0 | 1(7.7%) | 13.6%) | |
| Grade 4 | 0 | 0 | | |
| **Gastrointestinal toxicity** | | | | |
| Grade 0 | 3(20%) | 0 | 3(10.7%) | |
| Grade 1 | 8(53.3%) | 17.7%) | 9(32.1%) | 0.005 |
| Grade 2 | 2(13.3%) | 9(69.2%) | 11(39.3%) | |
| Grade 3 | 1(6.7%) | 3(23.1%) | 4(14.3%) | |
| Grade 4 | 1(6.7%) | 0 | 1(3.6%) | |

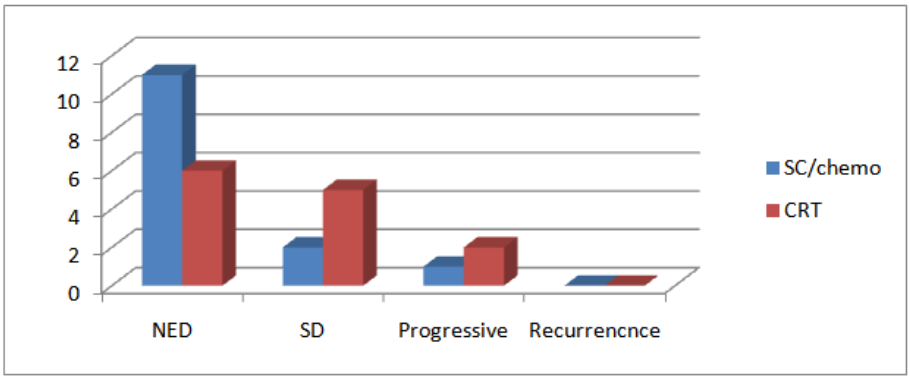
| | | | | |
|---|---|---|---|---|
| **Skin toxicity** | | | | |
| Grade 0 | 11(73.3%) | 0 | 11(39.3%) | 0.001 |
| Grade 1 | 4(26.7%) | 5(38.5%) | 9(32.1%) | |
| Grade 2 | 0 | 6(46.2%) | 6(21.4%) | |
| Grade 3 | 0 | 2(15.4%) | 2(7.1%) | |
| Grade 4 | 0 | 0 | 0 | |
| **Hand foot syndrome** | | | | |
| Grade 0 | 12(80%) | 10(76.9%) | 22(78.6%) | 0.843 |
| Grade 1 | 3(20%) | 3(23.1%) | 3(23.1%) | |
| **Proctitis** | | | | |
| Grade 0 | 9(60%) | 8(61.5%) | 17(60.7%) | |
| Grade 1 | 2(13.3%) | 2(15.4%) | 4(14.3%) | 0.292 |
| Grade 2 | 4(26.7%) | 1(7.7%) | 5(17.9%) | |
| Grade 3 | 0 | 2(15.4%) | (7.1%) | |
| Grade 4 | 0 | 0 | 0 | |

**Follow-up**

There was a median follow up of 6 months. There were a total of 28 patients, 13 in control arm and 15 in study arm (Table 4). 1 was lost to follow up in study arm, thus leaving 27 evaluable patients, 13 patients in control arm and 14 in study arm. 11 patient(73.3%) in study arm and 6 patients(46.2%) in control arm had no evidence of disease at median follow up of 6 months(p=0.142). 2 patients(13.3%) in study arm and 5 patients(38.5%) in control arm had stable disease(p=0.126). 1 patient in study arm(6.7%) and 2 patients in control arm(15.4%) had progressive disease(p=0.457). None of the patients in both the arms had recurrence.

**Table 4.**

| Follow up | Study arm (SC + chemo) | Control arm (CRT) | Total | p-value |
|---|---|---|---|---|
| **NED** | 11(73.3%) | 6(46.2%) | 17(60.7%) | 0.142 |
| **SD** | 2(13.3%) | 5(38.5%) | 7(25%) | 0.126 |
| **Progressive** | 1(6.7%) | 2(15.4%) | 3(10.7%) | 0.457 |
| **Recurrence** | 0 | 0 | 0 | |




## V. Discussion

Based on the current high level of evidence, the gold standard for treatment of stage II and III rectal cancer consists of neo-adjuvant combined modality therapy prior to TME, followed by postoperative chemotherapy. Conventionally fractionated chemoradiation with delayed surgery or 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 chemoradiation.

In addition, short-course irradiation is less expensive and more convenient, especially in centres with a large patient load. On the other hand, the use of high doses per fraction raises concern about late toxicity. Conventionally fractionated chemoradiation has been shown to be better than the short-course radiotherapy at reducing local recurrences. Another advantage of chemoradiation is better sphincter preservation. However, there is no firm evidence to support this.

The Capecitabine/5-FU based conventionally fractionated chemoradiation followed by surgery and adjuvant chemotherapy is considered as the standard in resectable rectal cancer.

In patients with locally advanced rectal cancer there is a substantial risk of treatment failure either locally or systemically and chemoradiation is the preferred regimen, since the addition of chemotherapy to conventionally fractionated radiotherapy improves local control and cancer-specific survival. Some recent reports have shown promising results with a strategy of delivering 5 Gy x 5 with delayed surgery[12,13,14]. These non-randomized studies support the notion that short-course preoperative radiation also results in down-staging if surgery is postponed. In addition, a Polish study in which patients were given 5*5Gy regimen followed by three cycles of FOLFOX-4 showed an improved overall survival and toxicity profile.

The Dutch Colorectal Group[15] treated 50 patients presenting with primary rectal cancer and synchronous resectable metastasis on a phase II trial of short-course radiation followed by six cycles of capecitabine plus oxaliplatin plus bevacizumab (restaging after two cycles),with resection of the primary and resection and/or ablation of the metastasis and it also showed an improved overall survival and toxicity profile.

Following evidence of tumour down-staging with short-course radiation and improved survival in these studies and arguments for neo-adjuvant chemotherapy there is a rationale for applying this concept on patients with rectal cancer at high risk of local or systemic failure.

Thus, with this background, this trial was conducted at the Department of Radiotherapy and Oncology, Regional Cancer Centre, IGMC, Shimla, to establish the efficacy of short course pre-operative RT followed by two cycles of consolidation chemotherapy in locally advanced ca rectum.

A total of 28 patients were enrolled, of these 1 patient was not evaluable for response due to reasons discussed earlier. Thus, total evaluable patients were 27, 15 in short-course RT arm and 13 in conventional CRT arm. All the patients were matched in both the arms with respect to patient characteristics and disease characteristics. All the patients completed treatment within stipulated time.

Surgery was performed 4-6 weeks after completion of treatment, in total of 16(57.1%) patients. Therefore, response could be assessed pathologically in only 16 patients. Of the patients who did not undergo surgery, 7(25%)refused surgery, 4(14.3%) were found inoperable, and 1(3.6%) was lost to follow up.

The response rates at first follow up were as follows: the pathological complete response was seen in the short course RT/chemotherapy arm in 1(6.7%) patient and in none of the patients in conventional CRT arm. 5(33.3%) patients in short course RT/chemotherapy arm and 7(53.8%) patients in conventional CRT arm had partial response. 8(53.3%) patients in short course RT/chemotherapy arm had stable disease and 6(46.2%) patients in the conventional CRT arm had stable disease. None of patients in both the arms had progressive disease.

In a phase III trial by Polish Colorectal Study Group, outcomes and toxicity between short-course radiation therapy/chemotherapy vs conventional chemoradiotherapy in 515 patients with stage cT3 or cT4 rectal cancer were compared. A short course of radiation (5 days) followed by 3 cycles of chemotherapy yielded comparable outcomes as those with conventional radiation with concurrent chemotherapy. Three-year disease-free survival was over 50% in each arm, and local failure rates were 22% per arm. Overall survival also appeared to favour the short-course approach.

In a phase II study by the Dutch Colorectal study Group, of the 41 patients who underwent surgery, 44% achieved a tumour regression grade of 0 to 2. This approach is being now being tested in the phase III setting.

The second end-point of the study was toxicity assessment. The most common observed toxicity was gastrointestinal toxicity, with grade 3-4 toxicity seen in 23.1% of patients in the conventional CRT arm and approximately 13.4% patients in the short course RT/chemotherapy arm(p=0.451).There was a trend towards lower gastrointestinal toxicity in the short course RT/chemotherapy arm and the difference between the two arms was statistically significant. Grade 3 hematological toxicity was seen in 1 patients in the conventional CRT arm i.e. 7.7% and in none of the patient in short course RT/chemotherapy arm. There was a trend towards lower hematological toxicity in the short course RT/chemotherapy arm and the difference between the two arms was statistically significant(0.006). Grade 3 proctitis was seen in 2(15.4%) patients in the conventional CRT arm and in none of the patient in short course RT/chemotherapy arm in our study, with no statistically significant difference (p=0.292). Grade 3 radiation dermatitis was seen in 15.4% of patients in conventional CRT arm and in none of patients in short course RT/chemotherapy arm in our study. No grade 4 radiation dermatitis was seen.

There was a trend towards lower skin toxicity in the short course RT/chemotherapy arm and the difference between the two arms was statistically significant (0.001). Grade 3-4 hand-foot syndrome was seen in none of the patients in our study. Overall there was a trend towards lower acute toxicities in the short course RT/chemotherapy arm with statistically significant difference.

In a phase III study by Polish Colorectal Study Group, the rates of acute events (73% vs. 81%) and toxicity-related deaths (1% vs. 3%) favoured the experimental arm over the control arm. Rates of grade 3+ toxicities, however, were essentially the same, 23% and 21%. Moreover, the need for radiotherapy dose reduction (0% vs. 8%; $p < 0.001$) or prolonged radiotherapy 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 addition in a phase II study by the Dutch Colorectal Study Group, no toxicity during radiation was reported. In our study also trend towards lower acute toxicities were seen in the study arm i.e. short course RT/chemotherapy.

In our study, R0 resection rates were comparable in both the treatment arms (87.5% in each arm). 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.

Thus in our study, the response rates and toxicities of short course RT/chemotherapy and conventional CRT were compared in the neo-adjuvant setting in locally advanced rectal cancer. The response rates were comparable in both the treatment arms. The rate of R0 resection was also comparable in both the treatment arms. The rates of gastrointestinal, skin and hematological toxicities were lower in the short course RT/chemotherapy arm with a statistically significant difference. Other toxicities between the two groups were found to be comparable.

## VI. Conclusion

The results from our study suggest that response rates in the two treatment arms are comparable. Major advantage for the short course radiotherapy followed by chemotherapy in neo-adjuvant setting was the improved toxicity profile compared with standard chemoradiation**.** Moreover short course RT regimen followed by chemothreapy is more convenient for the patients.

Thus, short-course RT followed by chemotherapy in the neoadjuvant setting can be used as an effective alternative to conventional CRT in locally advanced carcinoma rectum. However, as the sample size was very small, larger studies with longer follow-up need to be done to validate the results.

## Acknowledgement

We express our profound gratitude to all those who have enabled us in any way to complete this study and finally to all the patients of this study without whom this study would not have been possible.

## 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;37:73-87.
[2]. Phillips RK, Hittinger R, Blesovsky L, et al. Local recurrence following 'curative' surgery for large bowel cancer. I. The overall picture. Br J Surg 1984;71:12-6.
[3]. Kapiteijn E, Marijnen C, 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;24:528-35.
[4]. **4**.Gerard 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 ClinOncol 2006;24:4620–5.
[5]. Bosset JF, Calais G, Daban A, *et al*. Preoperative chemoradiotherapy *versus* preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance. *Eur J Cancer* 2004; 40: 219–224.
[6]. Marijnen CAM, Peetrs KCMJ, Putter H, *et al*. Long term results, toxicity and quality of life in the TME trial. *Radiother Oncol* 2004; 73(Suppl 1): S127–S128
[7]. Birgisson H, Pahlman L, Gunnarsson U, et al. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol* 2005; 23: 8697–8705.
[8]. Swedish Rectal Cancer Trial. Initial report from a Swedish multicentre study examining the role of preoperative irradiation in the treatment of patients with resectable rectal carcinoma. *Br J Surg* 1993; 80: 1333–1336.
[9]. Marijnen CAM, Kapiteijn E, van de Velde CJH, *et al*. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicentre randomized trial. *J Clin Oncol* 2002; 20: 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: 15–24.
[11]. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-646
[12]. Radu C, Berglund Å, Påhlman L, et al: Short course preoperative radiotherapy with delayed surgery in rectal cancer - a retrospective study. Radiother Oncol 2008, 87:343–349.
[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, 92:210–214.
[14]. Pettersson D, Holm T, Iversen H, et al: Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 2012, 99:577–583.
[15]. 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 ClinOncol 2010; 28:295(suppl 15; abstr 3638)

Niketa Thakur. " Long-Course Conventional Neoadjuvant Chemoradiotherapy Versus Short Course(5*5 Gy) Radiotherapy Followed By Consolidation Chemotherapy With Delayed Surgery In Locally Advanced Carcinoma Rectum: Results Of A Prospective Randomized Study."IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 3, 2018, pp 01-12.