ABSTRACT Aim: Colorectal cancer is the second most common cancer in women and third among men worldwide. The aim of this study is to assess radiological downstaging, pathological response, toxicity following short-course radiation therapy in the neoadjuvant treatment of locally advanced carcinoma rectum. Materials & methods: 20 Patients with locally advanced carcinoma rectum were studied by a prospective single-group Cohort Study. Target volumes were delineated using RTOG contouring guidelines. Short course radiotherapy with a dose of 25 Gy in 5 fractions, once daily for 5 days delivered using 3D conformal radiotherapy. The toxicity was assessed following radiation and during surgery. After 6 weeks, pelvic MRI was done and categorized according to MRI tumour regression grade. Surgery was done at 6-8 weeks. Pathological response assessed using Mandard tumour regression grade. Results: 66.67% of patients with T3N1 disease and 88.89 patients with T3N2 disease had statistically significant grade 3 tumour regression on MRI. 66.67% of patients with T3N2 disease and 50% with T3N1 disease attained statistically non-significant grade 3 pathological tumour regression. One T3N0 patient attained pathologic complete response. Most of the patients had grade1 or grade 2 toxicity. Findings: Tumour downstaging occurs when surgery is delayed by 6-8 weeks after short-course radiotherapy in T3N0/N+ locally advanced rectal cancers, with an acceptable toxicity profile.

KEYWORDS Chemoradiation, Short course Radiotherapy, Tumour Regression Grade

Introduction

Locally advanced rectal cancers are treated by chemoradiation followed by surgery. The two neoadjuvant approaches which have been studied extensively and found beneficial in improving local control are Long-Course Chemoradiation [1] and Short-Course hypofractionated Radiotherapy. LCRT refers to conventionally fractionated radiation therapy 45–50.4 Gy in 1.8–2.0 Gy fractions given 5 days per week with concurrent [2] 5-fluorouracil-based chemotherapy. SCRT typically involves a hypofractionated treatment of 25 Gy in 5 fractions once daily over 1 week.

Long-course chemo-radiation results in local control with a high rate of tumor regression with a significant rate of complete pathological response (pCR). Several RCTs have confirmed that this pCR is associated with a favourable outcome with respect to local control, distant recurrence, disease-free survival, and overall survival[3]. Short-course radiotherapy (SCRT) has been used with a different goal, i.e. “sterilizing” the irradiated area immediately before surgery without any expected reduction in the tumour’s stage and size. This is mainly due to the short
overall treatment time. ie surgery is done within one week of completion of radiotherapy. It is known that delaying surgery[4] for 6-8 weeks after radiation produces a significant rate of tumour regression[5]. Therefore the increase in the overall treatment time (by prolonging the interval between radiation and surgery) results in tumour regression and induces a higher complete response rate even in patients treated with SCRT. SCRT with early surgery results in lower pCR rates[5], lower severe acute toxicities, no difference in late toxicities, and no apparent difference in local control, disease-free survival, and overall survival[6] when compared with LCRT. When surgery is delayed after SCRT, cancer outcomes appear equivalent[7], including pCR rates. Studies[8] have shown that a 5×5 Gy schedule is well tolerated in elderly patients & those not fit for long course chemoradiation. Further, considering the advanced local stage, the schedule has considerable anti-tumour activity and can result in radical surgery in a high proportion of patients.

Objectives

Primary Objective
To assess the Tumour response (radiological downstaging & pathological response) following short-course radiation therapy.

Secondary Objective
To study the Toxicity profile (during & following radiotherapy).

Materials & Methods

20 Patients with locally advanced rectal carcinoma, attended Radiotherapy Department during December 2017 to August 2018 were selected.

Inclusion Criteria
1. Patients with locally advanced primary rectal cancer (stage II or III) (cT3N0, T3N+ and T4N0 not fit for long course chemoradiation)
2. Pathologically proven adenocarcinoma
3. Age < 75 years
4. ECOG performance status ≤ 2
5. Patients fit for major surgery

Exclusion Criteria
1. Distant metastases
2. Previous radiotherapy to the pelvis

Pretreatment evaluation includes
1. Informed written consent
   (a) History & physical examination including digital rectal examination
   (b) Blood analysis including CEA
2. Colonoscopy Biopsy, Chest X-ray
   (a) T and N stages were assessed using pelvic magnetic resonance imaging (MRI)

Radiotherapy treatment Planning
Patients were immobilized using a thermoplastic mask. Planning CT scans were taken as 3mm slices in supine position, after intravenous contrast administration. CT data was transferred to a Treatment Planning system (TPS Eclipse version 15.1) in Radiotherapy Department. Target volumes were delineated on CT scans according to RTOG contouring guidelines [9].

Clinical target volume (CTV) was delineated, including the gross tumour volume with margins (2–3 cm depending upon tumour position, defined by MRI imaging), the mesorectum and regional lymph nodes depending upon tumour location. Small bowel, femoral heads and bladder were contoured as critical organs.

Treatment approach
1. SCRT: 25 Gy in 5 fractions (Monday-Friday) delivered once daily using external beam linear accelerator by conformal radiotherapy 3DCRT.
2. Surgery was done at 6-8 weeks following radiotherapy.
3. Adjuvant chemotherapy started 4 weeks after surgery, with CAPEOX 3 weekly for 6 months. Inj Oxaliplatin 130 mg/m2 IV 500ml D3 over 2 hr T. Capecitabine 1000 mg/m2 BID PO 14days

Response assessment & follow-up
Pelvic MRI repeated at 6 weeks following radiation for evaluation of T and N stage, maximal wall thickness and categorized according to MRI tumour regression grading criteria[10]. Pathologic response assessed using Mandard[11] classification system’s tumour regression grade.

The toxicity was assessed at weekly intervals following radiation treatment, as well as during surgery and recorded according to the National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE).

Results

The age range of the study population was 40 to 70 years. The mean age of the patients was 58.95 years. Majority were males (65%). Most common clinical presentation was bleeding per rectum (55%) followed by constipation (25%). Most of the lesions were mid rectal tumours. The majority of the patients were T3 with perirectal lymph node-positive.

1. Toxicity profile
Anaemia was the most common adverse event seen, followed by diarrhoea and neutropenia. However, Grade 3 or 4 toxicity was rare. The treatment was well tolerated in all patients. Out of the 20 patients, 9 had grade 1 or 2 anaemia. Out of the 5 patients with diarrhoea, 4 had grade 1. Grade 1 neutropenia was seen with 4 patients, 7 patients complained of dysuria. Most of them had grade 1 symptoms (6 patients) followed by grade 2. None of the patients developed thrombocytopenia or skin reactions (Table 1).

2. MRI response assessment
65% of patients had grade 3 tumour regression, and 25% had grade 4 regression. 10% showed grade 2 regression in MRI.

All the patients underwent surgery at the stipulated 6–8 weeks following radiation treatment. Of the 20 patients, 55% underwent LAR, and 45% underwent APR.
### Table 1: Toxicity Analysis

| Toxicity       | Frequency | Percentage % |
|----------------|-----------|--------------|
| Diarrhoea      | 5         | 25           |
| Anemia         | 19        | 95           |
| Thrombocytopenia | 0       | 0            |
| Neutropenia    | 4         | 20           |
| Skin Reactions | 0         | 0            |
| Dysuria        | 7         | 35           |

### Table 2: Association Between Stage and MRI Response

| STAGE | MRI RESPONSE | Total |
|-------|--------------|-------|
|       | TRG 2 n (%)  | TRG 3 n (%) | TRG 4 n (%) |       |
| T3N0  | 1 (100)      | 0         | 0            | 1     |
| T3N1  | 1 (16.67)    | 4 (66.66) | 1 (16.67)    | 6     |
| T3N2  | 0            | 8 (88.89) | 1 (11.11)    | 9     |
| T4N0  | 0            | 1 (25)    | 3 (75)       | 4     |
| Total | 2            | 13        | 5            | 20    |

### Table 3: Association Between Stage and Pathological Response

| STAGE | PATHOLOGICAL RESPONSE | Total |
|-------|------------------------|-------|
|       | TRG 1 n (%)  | TRG 2 n (%) | TRG 3 n (%) | TRG 4 n (%) |       |
| T3N0  | 1 (100)      | 0         | 0            | 0            | 1     |
| T3N1  | 0            | 1 (16.67) | 3 (50)       | 2 (33.33)    | 6     |
| T3N2  | 0            | 2 (22.22) | 6 (66.67)    | 1 (11.11)    | 9     |
| T4N0  | 0            | 0         | 2 (50)       | 2 (50)       | 4     |
| Total | 1            | 3         | 11           | 5            | 20    |

### Table 4: Association Between MRI Response and Pathological Response

| MRI response | PATHOLOGICAL RESPONSE | Total N |
|--------------|------------------------|---------|
|               | TRG 1 n (%)  | TRG 2 n (%) | TRG 3 n (%) | TRG 4 n (%) |       |
| TRG 2        | 1 (50)       | 1 (50)      | 0            | 0            | 2      |
| TRG 3        | 0            | 2 (15.38)   | 10 (76.92)   | 1 (7.7)      | 13     |
| TRG 4        | 0            | 0           | 1 (20)       | 4 (80)       | 5      |
| Total        | 1            | 3           | 11           | 5            | 20     |

### Table 5: The comparison of the rate of Pathological complete response in various studies

| Study                  | Number of patients with pathological complete response / total number of patients (%) |
|------------------------|-------------------------------------------------------------------------------------|
| Stockholm III trial[13] | 15/120 (12.5)                                                                      |
| Hatfield [4]           | 2/24 (8)                                                                            |
| Pach[18]               | 8/77 (10)                                                                           |
| Radu[14]               | 2/28 (7)                                                                            |
| Latkauskas T[15]       | 3/75 (4.4)                                                                          |
| Our study              | 1/20 (5)                                                                            |

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3. Pathological response assessment

The response was assessed using the Mandard Tumour Regression grading system. One patient attained complete pathological response, 55% had grade 3 regression, 25% had grade 4 regression, and 15% had grade 2 tumour regression.

4. Statistical analysis

Data analysis was done with the help of Excel 2013 and analysed statistically using statistical package for the social services (SPSS) version 23 software.

A. Association between stage and MRI response

Association between stage of disease and MRI response was found to be statistically significant on Chi-Square Tests. 66.67% of patients with T3N1 disease and 88.89 patients with T3N2 disease had Grade 3 regression in MRI. (Table 2)

\(X^2 = 13.085, df = 6, p = 0.042\)

B. Association between stage and pathological response

Chi-square test analysis showed that the result was statistically non-significant. 66.67% of patients with T3N2 disease and 50% of patients with T3N1 disease attained grade 3 Pathological tumour regression. 33.31% of patients with T3N1 had Grade 4 regression. (Table 3)

\(X^2 = 11.431, df = 9, p = 0.247\)

C. Association between MRI response and pathological response

Statistically, a significant association was found on chi-square test analysis. 76.92% of patients who showed Grade 3 regression in MRI attained Grade 3 regression in the pathological examination. Similarly, 80% of grade 4 MRI response patients had pathological regression grade 4. Those who showed better tumour regression in MRI had similar pathological regression grade and was statistically significant. (Table 4)

\(X^2 = 18.749, df = 6, p = 0.005\)

Discussion

Rectal cancer is the third most common malignancy seen in men worldwide. Surgery with Total Mesorectal Excision is the preferred treatment modality. The addition of radiotherapy in neoadjuvant treatment of locally advanced rectal cancer resulted in a considerable reduction in local recurrence[12]. Traditionally long course chemoradiation is the standard of care in preoperative treatment. Short course radiation therapy with immediate surgery is considered in those patients in whom tumour downstaging is not required. Recent studies evaluated the role of short-course radiation therapy followed by delayed surgery at 6-8 weeks. Tumour downstaging occurred, and it was not associated with significant toxicity.

Hatfield et al. [4] studied patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. Treatment was well tolerated, although two patients required hospital admission for management of diarrhoea and one developed significant late small bowel toxicity. In those undergoing R0 or R1 resection, there have been no local recurrences (median follow-up 18 months).

The Stockholm III Trial[13] randomized patients with primary operable rectal cancers to either SCRT with immediate surgery, SCRT with surgery delayed 4–8 weeks, or long-course RT with surgery delayed 4–8 weeks. Patients randomized to SCRT-delay had earlier ypT categories and a higher rate of pCR(11.8 versus 1.7 per cent; P=0.001) and Dworak grade 4 tumour regression(10.1 versus 1.7 per cent; P <0.001) than patients randomized to SCRT without delay. Positive circumferential resection margins were uncommon (6.3 per cent) and rates did not differ between the two treatment arms.

Radu et al[14] reported that short-term radiotherapy and delayed surgery could give similar results as conventional CRT. Patients with non-resectable rectal cancer (+/-synchronous distant metastases) were treated with 5 × 5 Gy and delayed surgery. The clinical records were retrospectively evaluated. The first group (A) had no metastases (T4N × M0), whereas the other two groups (B+C) had metastases (T4N × M1). In group (B), the patients were not candidates for combination chemotherapy (high age, co-morbidities), and in group (C) up-front combination chemotherapy was given, with the intention to have surgery of both the primary and the secondaries if sufficient regression at both sites were seen. The 5 × 5 Gy RT was well tolerated by most patients, but grade IV diarrhoea was recorded in three elderly patients. One patient in the group (C) died from neutropenic fever. Many patients were reported to have fewer local symptoms after the treatment given. Delayed surgery was performed in all. Radical surgery (R0+R1) was performed in 22 (92%) (group A), 4 (44%) (group B), and 6 (46%) (group C) patients, respectively. A pCR was seen in four patients (two in group A and two in group C). No postoperative deaths occurred. Considering the very high age and presence of co-morbidity, the 5 × 5 Gy schedule is well tolerated and has considerable anti-tumour activity.

Latkauskas T et al. [15] compared preoperative conventional chemoradiotherapy versus short-course radiotherapy with delayed surgery for rectal cancer. 150 patients diagnosed with stage II–III rectal cancer were randomized into two arms: conventional chemoradiotherapy (CRT) and SCRT, followed by surgery after 6–8 weeks. Primary endpoints of this trial were downstaging and pCR. Secondary endpoints were local recurrence rate and overall survival. The pathological complete response was found in 3 (4.4%) cases after SCRT and 8 (11.1%) after CRT (P=0.112). Downstaging (stage 0 and I) was observed in 21 (30.9%) cases in SCRT group vs. 27 (37.5%) cases in CRT group (P=0.409). 3-years overall survival (OS) was 78% in RT group vs. 82.4% in CRT group (P=0.145), while disease-free survival (DFS) differed significantly–59% in RT group vs. 75.1% in CRT group (P=0.022). The conclusion was 3-year DFS was better in CRT group comparing with SCRT group with no difference in overall survival.

Biological effective dose [16] is also important in comparing SCRT to LCRT. The BED for acute responding tissues (α/β=10, BED10) of >30 Gy predicts LR. It is notable that 25 Gy in 5 fractions is neither isoeffective to 50 Gy in 25 fractions in terms of acute responding tissues nor late responding tissues (α/β=3) using the linear-quadratic formula. SCRT represents a BED10 of 37.5 Gy and BED3 of 66.7 Gy. The BED10 and BED3 for 50 Gy in 25 fractions is 60 Gy and 83.3 Gy, respectively. Considering daily repair and total treatment time, the BED10 of LCRT is 44.4 Gy. The inclusion of concurrent chemotherapy is expected to increase the BED10, but radiobiologic modeling of this effect in rectal cancer is limited. Randomized data clearly support the inclusion of concurrent chemotherapy with LCRT for the endpoint of LR[17].

In our study we analyzed a cohort of 20 patients with locally advanced rectal cancer to assess tumour downstaging, toxicity profile following SCRT with delayed surgery. The radiological response was evaluated using MRI Tumour Regression Grading.
65% patients had grade 3 tumour regression. 66.67% were T3N1 disease and 88.89% patients with T3N2 disease. The majority of patients with T4N0 had grade 4 regression. The difference was statistically significant. (p = 0.042).

Patients with a pCR after radiation have a significantly better long-term outcome than those with residual disease.pCR was assessed using the Mandard Tumour Regression grading system. In our study, 1 patient with T3N0 disease attained pCR. (Table 5)

66.67% of patients with T3N2 disease and 50% of patients with T3N1 disease attained grade 3 pathological tumour regression. 33.31% of patients with T3N1 had Grade 4 regression. However, the difference was not statistically significant. (p = 0.247). In our study, 76.92% of patients who showed Grade 3 regression in MRI attained Grade 3 regression in the pathological examination. Most of the patients who had grade 4 responses in MRI showed similar pathological grades. It was statistically significant. (p = 0.005)

Anaemia was the most common adverse effect, followed by diarrhoea and neutropenia. Most of the patients had grade 1 or grade 2 toxicity only. No hospitalization was required for the management of toxicity. Also, these adverse effects did not cause a delay in planned treatment.

Conclusion
Pathological response and toxicity profile were compared with available data. This study demonstrated that tumour downstaging occurs when surgery is delayed after SCRT and is a feasible option in T3N0/N+ locally advanced rectal cancers, with acceptable toxicity profile. Thus we can reduce long waiting period of patients in high volume centres like ours and thus create a positive impact in Radiation Oncology Department.

Abbreviations
3DCRT : Three dimensional Conformal Radiotherapy
5-FU : 5-fluorouracil
APR : Abdominoperineal resection
BED : Biological Effective Dose
CEA : Carcinoembryonic Antigen
CTCAE: Common Terminology Criteria for Adverse Events
CTV : Clinical target volume
ECOG : Eastern Cooperative Oncology Group
LCRT : Long-Course Chemoradiation
LAR : Low anterior resection
LR : Local Recurrence
MRI : Magnetic Resonance Imaging
NCI : National Cancer Institute
pCR : pathological complete response
RTOG : Radiation Therapy Oncology Group
SCRT : Short-Course Radiotherapy
SPSS : statistical package for the social services
TPS : Treatment Planning system

Ethics approval
The study was approved by The Institutional Ethics Committee, Govt Medical College, Kozhikode, (Ref.No.GMCKKD/RP2017/IEC / 250)

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Conflicts of interest
The author(s) declare none.

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