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RESEARCH ARTICLE

Acute Toxicities and Treatment tolerance of Neoadjuvant Chemoradiation in Rectal Cancer: A Tertiary Cancer Centre Analysis

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Abstract

Aims: To assess acute toxicities and treatment tolerance in patients of carcinoma rectum of NACTRT at a tertiary care centre of North-East India. **Materials and Methods:** A total of 50 patients of histologically proven Rectal Adenocarcinoma recruited from July 2022 to May 2023 were included in the study. All patients were planned for either NACTRT (n=44) or Total Neoadjuvant Treatment (TNT)(n=6) followed by assessment for surgery. A total dose of 50.4Gy/28# was planned with concurrent oral chemotherapy with T. Capecitabine at a dose of 825 mg/m^2 twice daily. Acute toxicities were assessed using RTOG grading criteria. Patients' toxicity assessment was done weekly with clinical examination and laboratory parameters. Patients were also assessed at the end of RT and 4 weeks post completion of NACTRT. **Results:** All patients could complete the prescribed dose of EBRT (50.4Gy/28#) over a period of 6 weeks. On toxicity assessment, Grade-I dermatitis was seen in 14 patients (56%), Grade-II in 14 patients (54%), Grade-III in 2 patients (7.6%). In lower gastrointestinal toxicities, Grade-I diarrhea occurred for 4 patients (50%), Grade-II diarrhea in 3 patients (37.5%) and Grade III diarrhea in 1 patient (7.6%). Grade-I genitourinary toxicity was observed in 4 patients (8%). Hematological toxicities were seen for 40 patients of which Grade-I, Grade-II, Grade-III Anemia were seen in 10 (38.4%), 14 (54%), 2 (7.6%) patients respectively. Grade 1 and Grade 2 leucopenia were seen in 4 (57%) and 3 (43%) patients respectively. Deranged LFT was seen for 7 patients (15%), out of whom dose modifications were required for 5 patients (10%). Treatment was put on hold for 3 patients (6%) for 3 days due to grade 3 toxicities. **Conclusion:** NACTRT in rectal cancer patients was associated with acceptable toxicities and treatment tolerance. Modern EBRT techniques like IMRT should be evaluated in an effort to further reduce the radiation related toxicities.

Keywords: Rectal cancer- Neoadjuvant Chemoradiation- Acute Toxicities

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Introduction

Neoadjuvant chemoradiation (NACTRT) followed by surgery and adjuvant chemotherapy is considered to be a standard treatment practice for clinically T3-T4 or node positive rectal cancers in many tertiary cancer centres [1, 2]. Current evidence also suggests the advent of Total Neoadjuvant Therapy (TNT) as a treatment option for locally advanced rectal cancer (LARC).

The addition of preoperative radiation along with 5-fluoro-uracil based chemotherapy has shown to improve the local control rates in LARC in many phase III studies [3, 4]. The toxicities of NACTRT were also found to be significantly less than adjuvant chemoradiation (CTRT) [5]. Even though radiation has lesser toxicities in the preoperative setting compared to the post operative period, the side effects can still be a limiting factor in the overall treatment tolerance or compliance of the patients. The combined effect of concurrent chemotherapy with radiation can further exacerbate the toxicities, resulting in increasing the overall treatment time of NACTRT and also delay the definitive surgery as well as adjuvant

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chemotherapy. Although techniques like Intensity Modulated Radiotherapy (IMRT) can reduce radiation induced toxicities compared to Three-Dimensional Conformal Radiotherapy (3DCRT) [6, 7], not all cancer centres employ IMRT as 3DCRT also has acceptable tolerance.

A large proportion of LARC is seen in our country, with colorectal cancers constituting almost 5% of all cancers in India [8]. The main aim of our study is to prospectively analyse the acute toxicities and treatment tolerance of NACTRT in LARC at a high-volume tertiary cancer centre in North Eastern region of India.

Materials and Methods

A total of 50 patients of histologically proven locally advanced Rectal Adenocarcinoma from July 2022 to May 2023 were recruited in the study. All patients were planned for either NACTRT (n=44) or Total Neoadjuvant Treatment (TNT) (n=6) followed by assessment for surgery and adjuvant chemotherapy. Informed consent was taken for all patients before starting the treatment. Patients were immobilised using pelvic thermoplastic mould. CT simulation was done for all patients in prone position with arms above head and a marker at anal verge. Proper bowel preparation with stimulant laxatives like bisacodyl was advised for all patients prior to the CT simulation. Bladder protocol was followed for all patients during the CT scan. The CT images were taken of the lower abdomen and pelvic region with 3mm slice thickness. The images were then transferred to Monaco and Eclipse TPS for radiation planning. External beam radiotherapy (EBRT) planning was done using 3DCRT technique using one posterior beam and two lateral beams (Figure 1) to a total dose of 50.4 Gray (Gy) in 28 fractions over five and a half weeks at 1.8 Gy per fraction. The given field ensured the coverage of the entire rectum, mesorectum and pelvic lymph nodal regions. Concurrent oral chemotherapy with Tab. Capecitabine at a dose of 825 mg/m^2 twice daily after food was prescribed along with radiation. A baseline clinical examination was done prior to starting radiation. Weekly review of patients for toxicity assessment and any required dose modifications of Capecitabine was done. Hematological investigations like complete blood count, kidney function tests, serum electrolytes and liver function tests were advised weekly during the review along with clinical examination. Radiation and capecitabine induced acute toxicities were assessed using RTOG (Radiotherapy and Oncology Group) [9] toxicity criteria. Patients were also assessed at the end of NACTRT and at 4 weeks post completion of NACTRT. Response assessment imaging with CECT/MRI whole abdomen was done at 4-6 weeks post completion of NACTRT. The response evaluation was done using RECIST 1.1 [10] Criteria.

Data collection and Analysis

The data of the patient characteristics, disease related specifications and toxicities during each review of all patients were collected and stored in Microsoft Excel. Descriptive statistics like percentages, mean and median were calculated.

Results

This was a prospective study with a sample size of 50 patients recruited from July 2022 till May 2023. The patient characteristics have been detailed in Table 1. The median age of the patients was 48.5 years with ages ranging from 16 to 80 years. The most frequent site of primary tumor was mid rectum (n=33), and most common histopathology was Well Differentiated Adenocarcinoma (n=25). Majority of the patients had clinical staging of AJCC stage III disease. NACTRT followed by surgery followed by adjuvant chemotherapy was planned 44 patients (78%) patients and TNT followed by surgery for 6 patients (12%).

All patients could complete the prescribed dose of EBRT (50.4Gy/28#) over a period of 6 weeks. Treatment was put on hold for patients (6%) for 3 days due to grade 3 toxicities.

The acute toxicities recorded are summarized in Table 2. The radiation induced toxicities that were assessed included skin toxicity (Figure 2), lower gastrointestinal tract toxicity and genitourinary toxicity. Grade I dermatitis was seen in 22 patients (44%), Grade II in 25 patients (50%), Grade III in 3 patients (6%). In lower gastrointestinal toxicities, Grade I diarrhea occurred for 4 patients (8%), Grade II diarrhea in 3 patients (6%) and Grade III diarrhea in 1 patient (2%). None of the patients had Grade IV dermatitis or Grade IV diarrhea. There was only Grade I genitourinary toxicity, which was observed in 4 patients (8%). After completion of NACTRT, patients were again assessed after 4 weeks. Majority of the toxicities were resolved, with 30 patients (60%) having grade 1 dermatitis, and 3 patients (6%) having grade 1 diarrhea at 4 weeks post NACTRT.

Hematological toxicities were seen in 80% of the patients (n=40). Grade I, Grade II, Grade III Anemia were seen in 10 (20%), 14 (28%), 2 (4%) patients respectively. Grade 1 and Grade 2 leucopenia were seen in 4 (8%) and 3 (6%) patients respectively. None of the patients had any significant neutropenia or thrombocytopenia. Deranged

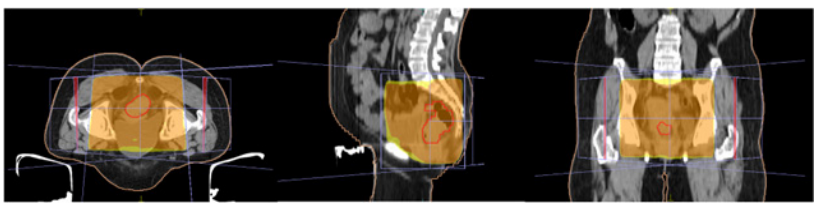

Figure 1. Three Field EBRT Planning Showing Dose Colour Wash of 50.4Gy in Axial, Sagittal and Coronal Sections (left to right)

Table 1. Patient and Treatment Details

Characteristic	Total (n=50)
Age (years)	
Range	16 – 80
Median	48.5
Gender	
Male	31
Female	19
Location of tumor	
Upper Rectum	5
Mid Rectum	29
Lower Rectum	12
Entire Rectum	4
HPE	
Well differentiated Adenocarcinoma	25
Moderately Differentiated Adenocarcinoma	14
Poorly Differentiated Adenocarcinoma	1
Mucinous Adenocarcinoma	5
Intramucosal Adenocarcinoma	3
Signet Ring Cell Adenocarcinoma	2
T (Tumor) stage	
T1	-
T2	4
T3	38
T4	8
N (Node) stage	
N0	16
N1	23
N2	11
N3	-
AJCC 8th Edition Staging	
Stage I	-
Stage II	6
Stage III	36
Stage IV	8
Radiation dose	50.4 Gy
RT Technique	3D-CRT
Concurrent chemo with Tab. Capecitabine @ 825 mg/m^2 BD (Total Dose per day)	
1500 mg	11
2000 mg	25
2500 mg	14

HPE – Histopathological Examination, AJCC - American Joint Committee on Cancer, Gy – Gray, 3D-CRT – Three-Dimensional Conformal Radiotherapy, BD – Twice daily

LFT was seen for 7 patients (14%), out of whom dose modifications were required for 5 patients (10%). All hematological toxicities were resolved at 4 weeks post completion of NACTRT.

Response assessment CECT/ MRI pelvis and abdomen was done in 36 patients (72%) at four to six weeks interval after completion of NACTRT (Table 2). Response evaluation was done using RECIST 1.1 criteria which showed that 3 patients (6%) had complete response, 22 patients (44%) had partial response, 8 patients (16%) had stable disease and 3 patients (6%) had progressive disease.

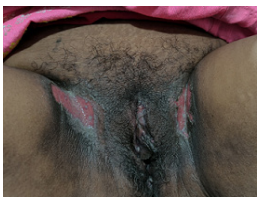

Figure 2. Grade II Dermatitis

Discussion

Colorectal cancers are the third most common cancer worldwide and second most common cause of cancer death, constituting ten percent of the newly diagnosed cancer cases [11]. The highest incidence and mortality rates are seen in the Asian continent compared to the rest of the world. Although Total Mesorectal Excision (TME) is the primary treatment modality of rectal cancers, the addition of NACTRT has shown improved locoregional control and sphincter preservation rates compared to surgery alone [1]. The addition of systemic chemotherapy addresses the micrometastases prevalent in these cancers, thereby reducing the distant failure as well as improving the overall survival [4, 12].

The entire course of treatment easily takes up to 9 to 12 months, assuming minimal treatment breaks and good compliance from patients. The protracted treatment of rectal cancers is challenging for the patients as multiple visits to the hospital as well as admissions are required. Our study aimed to assess the first step of this long treatment pathway, as any delays or increased toxicities in NACTRT would determine the further prolonging of the remaining management.

We have observed that our patients had minimal radiation induced toxicities (Table 2) that were less than what were seen in the existing literature [4]. Dermatitis is expected to occur in all patients as there are presence of skin folds and mucosal interface in the gluteal region. The use of 15 MV photons for the radiation planning resulted in lesser grade III dermatitis (6%) because of increased skin sparing effect. The lower G.I toxicities were also less frequent in these patients, with predominantly grade I diarrhea that could be due to irradiation of some portion of the large bowel. The prone position of the patient has resulted in lesser instances of diarrhea as the bowel bag falls anteriorly. The patients were treated with three field EBRT that included one posterior beam and two lateral beams. This could explain why only few patients had grade I genitourinary toxicity since there was no anterior component of EBRT that could irradiate bladder and external genitalia. Overall, the radiation induced toxicities did not lead to any significant treatment breaks as only 1 patient with grade III dermatitis required a gap of 3 days. All the toxicities were managed conservatively with supportive treatment, and none of the patients required

Table 2. Acute Toxicities and Response Assessment

Type of Toxicity	Total (n=50)
Dermatitis	
Grade I	16 – 80
Grade II	48.5
Grade III	
Diarrhea	
Grade I	31
Grade II	19
Grade III	
Genitourinary	
Grade I	
Anemia	
Grade I	25
Grade II	14
Grade III	1
Leucopenia	-
Grade I	4
Grade II	38
Response Assessment (RECIST 1.1)	Total (n=36)
Complete Response (CR)	3
Partial Response (PR)	22
Stable Disease (SD)	8
Progressive Disease (PD)	3

RECIST – Response Evaluation Criteria in Solid Tumors

in-patient admission.

The hematological toxicities due to concurrent Tab. Capecitabine were majorly limited to Grade I and Grade II toxicities. Patients with anemia received hematinics and blood transfusions as required. None of the patients developed hand-foot syndrome commonly seen in patients receiving capecitabine [13]. Weekly review of the blood parameters also ensured prompt dose modification if required in case of any intolerability of capecitabine. We observed that all chemotherapy related toxicities resolved after 4 weeks of completion of NACTRT. Overall, our patients had good tolerability of both radiation as well as concurrent oral chemotherapy.

Modern radiation techniques such as IMRT also play an important role in reducing the acute toxicities faced by the patients. A Korean meta-analysis by Chan et al showed that overall lower G.I toxicities was less in IMRT technique compared to 3DCRT techniques [14]. On the other hand, a few studies have shown no difference in patient reported toxicities between these two planning techniques [15]. Our study has used only 3DCRT planning for all patients and we have seen minimal grade 2 and grade 3 G.I toxicities. Although use of IMRT has been advocated by many researchers [14, 16], we have found similar toxicities with 3DCRT as seen with IMRT in the literature. This could be due to the fact of shielding of bowel bag with multi-leaf collimators (MLCs) and also due to the prone position of the patients. As there was no head on comparison of 3DCRT versus IMRT in our study, we do recommend a prospective study comparing these two modalities for a definite conclusion.

After completion of NACTRT, the response assessment scans that were advised at 4 to 6 weeks interval showed partial response in many patients. Various studies have shown the importance of complete resolution of the disease after neoadjuvant treatment that might also affect the overall survival [17]. In this study, only 6% of the patients had a complete response to NACTRT. However, not all patients had a response assessment imaging done during the analysis. As the primary aim of our study was acute toxicities, we have observed the patients only till the 4 to 6 weeks interval post radiation.

The main drawbacks of our study are the small sample size and the short follow up period of the patients. The information regarding subsequent surgery and adjuvant chemotherapy is not available for further review. The patients need to be followed up further for assessing the overall compliance, timely completion, and long-term toxicities of the entire course of management. We recommend conducting prospective studies with a larger number of patients assessing both acute and chronic radiation induced toxicities. Future research analysing the complete treatment along with the radiological as well as pathological responses will help us understand the current ramifications of the management of locally advanced rectal cancers.

In conclusion, NACTRT in rectal cancer patients was associated with acceptable toxicities, minimal treatment breaks and good tolerance in our study. Further follow up of patients is required to assess the successful completion of the remaining treatment with surgery and chemotherapy. The assessment of late toxicities of radiation would require a long term follow up of these patients. Modern EBRT techniques like IMRT should be evaluated in an effort to further reduce the radiation related toxicities. The authors suggest a larger sample size and comprehensive observation of the entire treatment course for a better understanding of the toxicity profile of rectal cancer patients.

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