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Treatment Outcome in Locally Advanced Rectal Carcinoma and Its Correlation with Hypo-Fractionated Radiotherapy and Concurrent Chemoradiotherapy

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Abstract **Introduction:** Rectal cancer is the second most common type within the large intestine, posing significant health risks globally. In Bangladesh, it ranks high among diagnosed cancers. Improved diagnostic methods aid in early detection, which is crucial for effective management. Treatment typically involves a combination of surgery, radiotherapy, and chemotherapy. Preoperative chemoradiotherapy is a standard approach. However, newer methods like preoperative hypo-fractionated radiotherapy with surgery promise better outcomes, including reduced recurrence rates and enhanced survival, with potential cost and time savings. **Aim of the Study:** The study aims to evaluate and contrast the efficacy of hypofractionated radiotherapy and concurrent chemoradiotherapy, in patients with locally advanced rectal carcinoma. **Methods:** The study, conducted at the Department of Clinical Oncology at Bangabandhu Sheikh Mujib Medical University Shahbagh, Dhaka, Bangladesh and the Department of Radiation Oncology at the National Institute of Cancer Research and Hospital (NICR&H) in Mohakhali, Dhaka, Bangladesh, aimed to compare treatments for locally advanced rectal cancer over 1.5 years (From January 2018 to June 2019). A total of 80 patients were divided into two groups; Group A received hypofractionated radiotherapy, while Group B received oral capecitabine alongside external beam radiotherapy. Inclusion criteria involved confirmed adenocarcinoma within specified stages, with ethical clearances obtained. Patients underwent evaluations before treatment and response assessments posttreatment. Treatment modalities were defined, focusing on radiotherapy and chemotherapy. Data were analyzed using SPSS software, employing various statistical tests. Results aimed to address study objectives while minimizing biases. **Result:** The study involved 80 patients, divided into Groups A and B, each with 40 individuals. Group A mainly comprised individuals aged 41-50 (45%), followed by 31-40 (25%). Group B had the highest proportion aged 31-40 (30%) and 41-50 (32.50%). Both groups showed male predominance (1.3:1). Moderately differentiated tumors were common, with Group A having more poorly differentiated tumors. Stage III was predominant pre-treatment (65% Group A, 70% Group B). Most patients presented with per rectal bleeding (80%) and alteration of bowel habits (56.25%). Response rates to treatment were similar between groups. Tumor downsizing was more frequent in Group B. Sphincter-sparing surgery was feasible in both groups with no significant difference. **Conclusion:** The study comparing preoperative hypofractionated radiotherapy (RT) to concurrent chemoradiotherapy (CCRT) for locally advanced rectal carcinoma found similar efficacy in tumor response, downsizing, and sphincter preservation. Statistical analysis showed no significant differences. Both approaches showed acceptable short-term outcomes, offering clinicians options based on patient and resource considerations.

Key Words hypo-fractionated, radiotherapy, chemoradiotherapy, surgical treatment and rectal carcinoma

Important

Key findings:

The study compared hypofractionated radiotherapy and concurrent chemoradiotherapy for locally advanced rectal carcinoma in 80 patients. Both treatments showed similar efficacy in tumor response and sphincter preservation, with acceptable short-term outcomes, offering clinicians options based on patient and resource considerations.

What is known and what is new?

The abstract provides insights into the known challenges and established treatments for rectal cancer, highlighting its global prevalence and the importance of early detection through improved diagnostic methods. It underscores the standard approach of preoperative chemoradiotherapy in managing the disease. The novelty lies in the comparison between two treatment modalities, hypofractionated radiotherapy and concurrent chemoradiotherapy, in a cohort of 80 patients with locally advanced rectal carcinoma. This study evaluates their efficacy in tumor response and sphincter preservation, revealing comparable outcomes between the two approaches. Such findings suggest potential alternatives for clinicians, considering individual patient needs and available resources.

What is the implication, and what should change now?

The abstracts suggest comparable efficacy between hypofractionated radiotherapy and concurrent chemoradiotherapy for rectal cancer, implying a need to consider these alternatives in treatment strategies to enhance patient care within existing resource constraints.

1. Introduction

Rectal cancer ranks as the second most prevalent type of cancer affecting the large intestine, comprising 28% of cases, with proximal colon cancers being the most common at 42% [1]. Hence, rectal cancers have consistently been included as a component of colorectal cancers (CRCs) in epidemiological studies. CRC, recognized as a significant public health concern, ranks as the third most prevalent cancer among men and the second most common among women globally, with an estimated lifetime risk ranging from 4.7% to 5% [2]. In Bangladesh, colorectal cancer ranks as the sixth most commonly diagnosed cancer in males and the ninth in females [3]. Advancements in diagnostic techniques such as recto sigmoidoscopy and new imaging modalities have facilitated the earlier detection and diagnosis of these cancers, enabling more timely intervention and improved management strategies [4]. Thorough evaluation of the primary tumor, nearby lymph nodes, and distant metastases is crucial for enhancing survival rates in rectal cancer, as it enables the selection of optimal treatment approaches. This involves effectively integrating three key treatment modalities: surgery, radiotherapy, and chemotherapy [5], [6]. At present preoperative concurrent chemoradiotherapy followed by surgery is practiced worldwide for treatment of advanced rectal cancer. Although this approach aims to diminish tumor size, impede tumor invasion, enhance the likelihood of tumor resection, and preserve anal function, it is costly as well as more time consuming for both patient and oncology team [7], [8]. However, multiple randomized trial showed a down staging effect, decreased local recurrence rate, increase overall survival, oncologic and functional outcome, cost-effectiveness, shorter treatment duration with preoperative hypo-fractionated radiotherapy with curative surgery which is at present one of the popular treatments [9]–[11]. The study aims to evaluate and contrast the efficacy of hypofractionated radiotherapy and concurrent chemoradiotherapy, in patients with locally advanced rectal carcinoma.

2. Materials and Methods

This is a multi-centre quasi-experimental study conducted at the Department of Clinical Oncology at Bangabandhu Sheikh Mujib Medical University Shahbagh, Dhaka, Bangladesh and the Department of Radiation Oncology at the National Institute of Cancer Research and Hospital (NICR&H) in Mohakhali, Dhaka, Bangladesh. The study spanned one and a half years, from January 2018 to June 2019. Utilizing a convenient type of non-probability sampling, a total of 80 patients meeting the specified criteria were selected, with 40 patients allocated to each of the two groups. Patients with clinically and histologically confirmed locally advanced adenocarcinoma of rectal cancer (Stage II-Stage III) and tumour located within 12 cm from the anal verge on colonoscopy patients were eligible for enrollment. Informed consent was obtained from each participant prior to their inclusion in the study. Patients with distant metastases, prior chemotherapy or radiotherapy cases ,initial surgery (excluding diagnostic biopsy) of the primary site, pregnant or lactating woman, dropped out or lost to follow-up before completion of study, poor performance status Eastern Cooperative Oncology Group (ECOG) score>2 and serious concomitant medical illness, including severe heart disease, uncontrolled diabetes mellitus, hypertension or renal diseases, uncontrolled infection were excluded from this study.The selected patients were divided into two groups, each receiving the specified treatment regimen. **Group A (N=40):** One group was treated with hypofractionated radiotherapy in a neoadjuvant setting. **Group B (N=40):** Another group was treated with an oral capecitabine tablet concurrent with external beam radiotherapy (EBRT) as a neoadjuvant chemotherapeutic agent.An ultrasonogram (USG), Computed Tomograpy scan (CT), or Magnetic Resonance Imaging (MRI) of the whole abdomen was done after four weeks of treatment as and when required. Treatment response evaluation was done using Response Evalution Criteria for Solid Tumors (RECIST) after two weeks of completion of preoperative hypofractionated radiotherapy (Group A) and four weeks of completion of chemoradiotherapy (Group B) and advised for surgery after a week in Group A and 6-8 weeks in Group B. Patients were also under follow up after surgery to see the treatment response.

3. Results

The research involved 80 patients in total. Group A consisted of 40 individuals, with the majority falling between 41 and 50 (45.00%). Following this, individuals aged 31-40 accounted for 25.00% of the group, and only one patient was from the age group of 61-70 years. Similarly, Group B, comprising 40 individuals, showed the highest proportion in the 31-40 age range (30.00%), and 32.50% were from the age group of 41-50 years, respectively. In this study, male predominance

was seen in both groups compared to females and the male –to-female ratio overall was 1.3:1. Most tumor grades were moderately differentiated, accounting for 52% and 55.50% in Groups A and B, respectively. Poorly differentiated tumors were more common in Group A (31.8%) than in Group B (22.8%) . In Group A, T3N0 was the most prevalent Tumor, Node, Metastasis (TNM) stage, comprising 15.00% of cases, followed by T3N1 and T4N1, representing 17.50% and 15.00% of the group. In Group B, T3N0 was also the most common TNM stage, constituting 25.00% of cases, followed by T4N1, which represented 22.50% of the group . 65% and 70% of Group A and B patients were in stage III pre-treatment. In total, 54 patients were in stage III (Table 1). Table 2 shows the clinical presentation of the study population, where most patients presented with per rectal bleeding (80%) followed by alteration of bowel habits (56.25%). Some patients presented with loss of appetite, urinary problems, pelvic pain, and rectal discomfort (26.25%). Four patients (10%) showed a complete response in Group A, whereas five patients (12.5%) did in Group B. Partial response rates were 70% and 72.5% in Group A and Group B, respectively, while stable disease rates were 20% and 14%, respectively. The p-value (0.948) was non-significant (>0.05). Two patients (5%) in Group A and 2 (5%) in Group B had a complete reduction of tumor size (T0) after preoperative RT and CCRT. T4-size tumors were seen in 10% of Group A and 5% of Group B. Fisher's Exact test yielded a non-significant p-value of 0.193 (>0.05) . Tumor downsizing was observed in 37 (84.1%) patients in Group B and 33 (75%) in Group A. Although the p-value was non-significant (>0.05), Group B showed more tumor downsizing numerically (Table 3). Two patients (5%) in Group A and 4 (10%) in Group B exhibited complete pathological responses, with a non-significant p-value (>0.05) of 0.395. Sphincter-sparing surgery was feasible in 28 (70%) patients in Group A and 27 (67.5%) patients in Group B, with a non-significant p-value (0.809) (>0.05) (Table 4).

Table 1 presents the distribution of patients based on epidemiological characteristics, pre-treatment grading, and pre-treatment TNM staging in both Group A and Group B. In Group A (N=40), age distribution shows 10% aged 21-30, 25% aged 31-40, 45% aged 41-50, 17.5% aged 51-60, and 2.5% aged 61-70. In Group B (N=40), age distribution is 10% aged 21-30, 30% aged 31-40, 32.5% aged 41-50, 20% aged 51-60, and 7.5% aged 61-70. Gender distribution indicates 57.5% males and 42.5% females in Group A, while Group B shows 55% males and 45% females. Tumor grading demonstrates 15% well-differentiated, 52.5% moderately differentiated, and 32.5% poorly differentiated tumors in Group A, compared to 22.5%, 55%, and 22.5%, respectively, in Group B. TNM staging reveals varying proportions of T2N1, T2N2, T3N0, T3N1, T3N2, T4N0, T4N1, and T4N2 stages in both groups. In terms of disease stage, 35% are Stage II and 65% are Stage III in Group A, while 30% are Stage II and 70% are Stage III in Group B.

4. Discussion

Colorectal cancer is ranked as the 3rd most common cancer in both male and female in worldwide [12]. In Bangladesh, rectal cancer is the 8th most common cancer and also the 6th leading cause of incidence in male and 9th in female [13]. Management of rectal cancer depends on staging, patient factor and others. Though surgery is the mainstay of curative treatment, it requires a multidisciplinary approach. For locally advanced rectal cancer, it has become established after a randomized trial by the German Rectal Cancer Study Group, who showed that neoadjuvant chemoradiotherapy in comparison to postoperative chemoradiotherapy provided a similar overall survival rate but a lower rate of local recurrence and toxicity [14]. Also, the important target of preoperative radiotherapy in locally advanced rectal cancer is to achieve local tumor control as well as to improve the chances of sphincter preservation inpatients initially considered for Abdominoperineal Resection (APR) a randomized trial by Swedish rectal cancer study group. Diagnosed patients of locally advanced rectal carcinoma (stage II and III) of adenocarcinoma cell variety were enrolled in this study. Total patients were 80 in number. Patients were divided equally in two groups. Group A received preoperative hypofractionated RT and Group B received oral capecitabine concurrently with external beam radiotherapy The present study findings discussed and also compared with previous relevant studies. In the present study age ranges from 21 to 70 years and most of the patients were in 41-to-50-year age group, 30 in number. The youngest patient was 21 years old and the eldest was 68 years. This is consistent with a cancer registry report (2014) that showed the peak incidence occurs at 41-50 years [13]. In this study male patient were found dominant in both Groups. The percentage of male patient in Group A and Group B were 57.9% and 54.5% respectively, whereas the percentage of female patients were 43.1% and 45.5% respectively. The male and female ratio in total was 1.3:1 indicating predominantly male, which is relevant to cancer registry report (2014) that showed male and female ratio 1.4:1 [13]. Most of the tumor grading was moderately differentiated, 52% in Group A and 55.5% in Group B respectively which is comparable to Yoney and Isikli, 2014 [15]. Most of the patients were T4N0 in Arm A (17.5%) and T3N0 in Arm B (25%). In this study patients with locally advanced carcinoma of rectum were enrolled. Majority of the patients' pretreatment clinical staging was Stage III (67.5%). In Group A, it was 65% and in Group B, it was 70%. In this study, the majority of patients presented with per rectal bleeding (80%) followed by alteration of bowel habit (56.25%). Some patients presented with loss of appetite, urinary problems, pelvic pain and rectal discomfort (26.25%). These clinical findings had concordance with the findings by Hamilton et al.,2005 [16]. Toxicities were regularly observed in this study during and after preoperative RT and CCRT. After completion of preoperative RT and CCRT treatment, response evaluation was done after four weeks by clinical examination and imaging according to follow up schedule which was set earlier. Complete response (CR) was

Variables	Group A (N=40) %		Group B (N=40) %	
Age (years)				
21-30	4	10.00	4	10.00
31-40	10	25.00	12	30.00
41-50	18	45.00	13	32.50
51-60	7	17.50	8	20.00
61-70	1	2.50	3	7.50
Gender				
Male	23	57.50	22	55.00
Female	17	42.50	18	45.00
Tumor grading				
Well differentiated	6	15.00	9	22.50
Moderate differentiated	21	52.50	22	55.00
Poor differentiated	13	32.50	9	22.50
TNM stage				
T2N1	2	5.00	3	7.50
T2N2	1	2.50	1	2.50
T3N0	6	15.00	10	25.00
T3N1	7	17.50	5	12.50
T3N2	6	15.00	4	10.00
T4N0	7	17.50	3	7.50
T4N1	6	15.00	9	22.50
T4N2	5	12.50	5	12.50
Stage of the disease				
Stage II	14	35.00	12	30.00
Stage III	26	65.00	28	70.00

Table 1: Distribution of patients according to the epidemiological characteristics , pre treatment grading and pre treatment TNM staging in both Group

Clinical Presentation	Percenage (%)
Per rectal bleeding	81.25%
Alteration of bowel habit	56.25%
Tenesmus	31.25%
Mucus discharge	12.50%
Others	26.25%

Table 2: Perntage of both Group of patients according to the frequency of clinical presentation

observed in 4 (10%) patients in Group A and 5 (12.5%) patients in Group B and partial response (PR) were 70% and 72.5% in Group A and Group B respectively. Only 8 (20%) patients in Group A and 6 (14%) patients in Group B had stable disease. There was no progressive disease in both Groups. Statistical analysis revealed there was no significant difference (p=0.734) but arithmetically this is proven that Group B patients had better response than Group A. 4 (10%) patients in Group A and 5 (12.5%) patients in Group B had complete reduction of tumor size (T0) after preoperative RT and CCRT. T4 size tumor was 10% in Group A and 5% in Group B. p-value was non-significant (>0.05). 33 (82.5%) patients in Group B and 73 (92.5%) patients in Group A had downsizing of tumor. Though p-value was non- significant (>0.05), numerically Group B had more downsizing of tumor and is supported by Kunheri et al., 2016 [17]. After completion of preoperative RT and CCRT treatment and follow up, all patients were advised for definitive surgery. Among them, pathological complete response was found more in Group B, i.e. 2 (5%) vs. 4 (10%), though p-value was non-significant (0.676). Sphincter sparing surgery was possible in 28 (70%) patients in Group A and 27 (67.5%) patients in Group B. Though the result was not statistically significant (p = 0.257), sphincter preservation was done more in Group A numerically. The study result is also supported by Allegra et al., 2015; O'Connell et al., 2014 and Yoney and Isikli, 2014 [18]–[20]. After careful analysis of the above data, it is very much evident that the present study could not demonstrate any significant differences about short-term tumor responses, tumor size reduction and sphincter sparing surgery between preoperative RT and CCRT were arithmetically equal. No significant difference between them (p value >0.05).

5. Limitations of the Study

The study has several limitations worth considering. Firstly, the study design, being quasi-experimental, lacks the robustness of a randomized controlled trial, potentially introducing bias and limiting the generalizability of findings. Secondly, the relatively small sample size of 80 patients may restrict the statistical power to detect significant differences between treatment groups, especially for less common outcomes. Additionally, the short duration of follow-up, spanning one and a half years, may not capture long-term treatment outcomes such as recurrence rates and overall survival. Moreover, the study's focus on a single geographical location, Bangladesh, may limit the applicability of findings to broader populations with differing demographics and healthcare systems. Finally, the absence of blinding in treatment allocation and outcome assessment could introduce bias into the results. These limi-

Variables	Group A (N=40) %		Group B (N=40)%		P value
Treatment response (after 4weeks)					
Complete response	4	10.00	5	12.50	0.948
Partial response	28	70.00	29	72.50	
Stable disease	8	20.00	6	15.00	
Tumor size					
T0	2	5.00	2	5.00	0.193
T1	5	12.50	13	32.50	
T2	17	42.50	10	25.00	
T3	12	30.00	13	32.50	
T4	4	10.00	2	5.00	
Downsizing of tumor					
Yes	33	82.50	37	92.50	0.176
No	7	17.50	3	7.50	

Table 3: Distribution of patients on the basis of post RT and CCRT treatment response ,tumor size reduction and downsizing of tumor in both Group

Variables	Group A (N=40) %		Group B (N=40) %		P value
Pathological complete response					
Yes	2	5.00	4	10.00	0.395
No	38	95.00	36	90.00	
Yes	28	70.00	27	67.50	0.809
No	12	30.00	13	32.50	

Table 4: Distribution of patients according to pathological complete response and sphinter preservation in both Group

tations underscore the need for larger, randomized controlled trials with longer follow-up periods to provide more robust evidence on the efficacy and adverse effects of different treatment modalities for locally advanced rectal carcinoma.

6. Conclusion and Recommendations

In conclusion, this study on locally advanced rectal carcinoma treatment demonstrated comparable efficacy between preoperative hypofractionated radiotherapy (RT) and concurrent chemoradiotherapy (CCRT) followed by surgery. Despite numerical variations in certain parameters, including treatment response, tumor downsizing, and sphincter preservation, statistical analysis did not reveal significant differences between the two groups. Both treatment modalities exhibited acceptable short-term tumor responses, tumor size reduction, and feasibility of sphincter-sparing surgery. These findings suggest that both approaches can be considered effective options in the management of locally advanced rectal carcinoma, providing clinicians with valuable insights for tailored treatment decisions based on patient characteristics and resource availability. Further long-term studies are warranted to assess their comparative long-term outcomes and toxicity profiles.

Conflict of interest

The authors declare no conflict of interests. All authors read and approved final version of the paper.

Authors Contribution

All authors contributed equally in this paper.

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