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Original Research Article

Effect of neoadjuvant concurrent three-dimensional conformal chemoradiotherapy with conventional two-dimensional chemoradiotherapy in locally advanced rectal cancer

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ABSTRACT

Background: Rectal carcinoma is a prevalent clinical condition, and treatment hinges on factors like tumor specifics, staging, grading, and histopathological characteristics. While surgery remains the primary treatment, neoadjuvant chemoradiotherapy, particularly using 3D-CRT, has proven effective in reducing local recurrence rates for locally advanced cases. Alternatively, 2D-RT is considered for neoadjuvant treatment. This study aimed to compare the impact of neoadjuvant concurrent three-dimensional conformal chemoradiotherapy with conventional two-dimensional chemoradiotherapy in the context of locally advanced rectal cancer.
Methods: In this multicentre quasi-experimental study, 60 patients with biopsy-proven adenocarcinoma and clinically confirmed locally advanced rectal cancer, were divided into Group A (receiving oral capecitabine with three-dimensional conformal radiotherapy) and Group B (receiving the same capecitabine dose with 50 Gy two-dimensional radiotherapy). After surgery within 6-12 weeks, outcomes were analysed.
Results: After neoadjuvant chemoradiotherapy, clinical complete response rates were 16.7% in Group A and 10.0% in Group B, with a higher pathological complete response in Group A (10.0% vs. 3.3%). Tumor downsizing occurred in 83.3% of Group A and 73.3% of Group B, and sphincter-sparing surgery was achieved in 73.3% of Group A and 56.7% of Group B. Grade 2 toxicities included anemia (10.0% vs. 13.3%), leucopenia (13.3% vs. 20.0%), diarrhoea (10.0% vs. 16.7%), proctitis (13.3% vs. 40.0%), and urinary toxicity (10.0% vs. 20.0%). Grade-1 toxicities were nausea (20.0% vs. 40.0%), vomiting (20.0% vs. 36.7%), mucositis (56.7% vs. 60.0%), hand-foot syndrome (33.3% vs. 40.0%), and urinary toxicity (43.3% vs. 56.67%), with significant proctitis in Group A (p=0.012). Other toxicities showed non-significant p-values (>0.05).
Conclusions: Tumour response was not statistically significant between the patients of concurrent 3D-CRT and 2D-RT Arms. But the patients of 3D-CRT arm showed better response arithmetically. Also, there was an observable significant reduction of toxicities (lower gastrointestinal) in the 3D-CRT arm.

Keywords: Chemoradiotherapy, Neoadjuvant, Radiation, Rectal cancer, Toxicity

INTRODUCTION

Cancer is a major cause of morbidity and mortality among non-communicable diseases in Bangladesh. In Bangladesh, cancer ranks as the sixth leading cause of mortality, and over half of cancer patients succumb within five years of diagnosis.[1] The number of people developing cancer is expected to increase significantly due to an aging population and lifestyle factors. The cancer load exceeds 1,200,000, with the number projected to increase substantially by 2030 in Bangladesh.[2] Colorectal cancer incidence and mortality rates have stabilized or declined in historically high-risk areas, while Japan, Korea, and China are experiencing a rapid increase.[3] This shift may be attributed to changes in risk factors and the adoption of colorectal screening, especially colonoscopy, which prevents cancer by removing precancerous lesions. Among adults aged 50 to 70 years, colonoscopy use increased from 19.1% in 2000 to 54.5% in 2013 among men. This increase in screening, irrespective of gender, race, and ethnicity, has contributed to improved 5-year survival rates, indicating the impact of colonoscopy and polypectomy on colorectal cancer outcomes.[4] Colorectal cancer is influenced by both environmental and genetic factors. Elevated risk is associated with factors such as high consumption of red meat and saturated fats, excessive alcohol intake, smoking, sedentary lifestyle, obesity, and diabetes. Adenomatous polyposis coli (APC) gene mutations are prevalent in familial colorectal cancer cases.[5] Adopting a "Mediterranean diet" with a high intake of vegetables, fruits, nuts, fish, cereals, and legumes, along with moderate alcohol consumption and low dairy and meat intake, is recognized as a health-protective measure against colorectal cancer.[6] The mesorectum encompasses the blood supply and lymphatics for the upper, middle, and lower rectum, serving as a reference in defining Total Mesorectal Excision (TME).[7] The rectal wall comprises four layers: mucosa, submucosa, muscle coat, and serosa. The peritoneum covers only the proximal one-third of the rectum, while the mid and lower rectums lack peritoneal covering. The Valves of Houston are three mucosal folds extending into the rectal lumen. The dentate or pectinate line marks the transition between columnar rectal mucosa and squamous anoderm, surrounded by columns of Morgagni, longitudinal mucosal folds.[8]

In rectal cancer, clinical staging increasingly guides decisions on initiating neoadjuvant chemoradiation therapy, emphasizing the crucial accuracy of the initial staging for effective management and prognosis.[5] Neoadjuvant treatment is preferred in scenarios requiring tumor shrinkage before surgery, such as locally advanced T4 disease and low-lying tumors aiming for sphincter preservation.[9]

This study aimed to compare the impact of neoadjuvant concurrent three-dimensional conformal chemoradiotherapy with conventional two-dimensional chemoradiotherapy in the context of locally advanced rectal cancer.

METHODS

This multicenter quasi-experimental study was conducted from Jan 2019 to June 2020. A total of 60 cases who had biopsy-proven adenocarcinoma and clinically confirmed locally advanced rectal cancer with no history of previous treatment were enrolled in this study as the study populations. The ethical clearance of the study taken from Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Participants were divided into two groups: Group A, treated with oral capecitabine tablet concurrent with three-dimensional external beam radiotherapy, and Group B, treated with oral capecitabine tablet concurrent with two-dimensional external beam radiotherapy. Sample selection employed a convenient and purposive sampling technique. Ethical approval was obtained from the hospital's ethics committee, and written consent was secured from all participants before data collection.

Inclusion criteria

Inclusion criteria specified patients diagnosed with locally advanced adenocarcinoma of the rectum, clinical TNM staging (stage II or III), and the tumor located within 10 cm from the anal verge on colonoscopy, as determined by CT scanning or MRI were included.

Exclusion criteria

The exclusion criteria for this study encompassed individuals unwilling to participate, those with distant metastases, different tumor types than adenocarcinoma, age below 18 years or above 70 years, prior surgery (excluding diagnostic biopsy) of the primary site, patients with double primaries, poor performance status (ECOG score >2), and a family history of rectal cancer diagnosed as hereditary nonpolyposis colorectal cancer.

Statistical analysis

Comprehensive demographic and clinical information for participants was documented and processed using MS Office and SPSS version 23.0. Statistical significance was set at a P value <0.05.

RESULTS

In the age comparison between the two groups, the mean age of patients was 45.200±11.589 years in Group A and 42.433±11.340 years in Group B, with a total mean age of 43.816±11.451 years. The t-value was 0.935. Regarding gender distribution, 56.66% of patients in Group A were male, while 63.33% were male in Group B. In the analysis of tumor distance distribution in both groups, the majority of tumors were 4 cm from the anal verge in Group A and 3 cm in Group B. No significant difference was found between the two groups (p>0.05). In terms of tumor grading, the majority of tumors were moderately differentiated, accounting for 53.3% in Group A and 60% in Group B. Well-differentiated tumors were more

prevalent in Group A (26.7%) than in Group B (23.3%). No significant difference was observed between the two groups (p>0.05). All toxicities were effectively managed through conservative treatment, and no treatment discontinuation or hospitalization for toxicity management was required throughout the treatment and follow-up period. There was no significant difference observed between the two groups (p > 0.05). In Group B, 66.7% of patients undergoing chemoradiotherapy experienced grade-1 hand-foot syndrome, compared to 60.0% in Group A. The difference was non-significant (p < 0.05). During treatment, radiotherapy-induced proctitis grade-2 toxicity in 13.3% of patients in Group A and 40.0% in Group B. Grade-1 toxicity was more prevalent, affecting 43.3% in Group A and 46.7% in Group B. A Fisher's Exact Test revealed a significant p-value (<0.05), specifically 0.012. The distribution of patients with radiation-induced urinary toxicity showed that 43.3% of patients in Group A and 56.67% in Group B developed grade-1 urinary symptoms, which were managed conservatively. The p-value was non-significant (>0.05).

After concurrent chemoradiotherapy (CCRT), it was observed that 16.7% of patients in Group A and 10.0% in Group B achieved a complete reduction of tumor size (T0). T4 size tumor was found in 10.0% of patients in Group A and 3.3% in Group B. Fisher's Exact test was performed, and the p-value was non-significant (>0.05). In our study, complete pathological responses were observed in 10.0% of patients in Group A and 3.3% in Group B. Fisher's Exact Test was performed, and the p-value was non-significant. Sphincter-sparing surgery was feasible in 22 (73.3%) patients in Group A and 17 (56.7%) patients in Group B, with a non-significant p-value (>0.05). The overall sphincter-sparing surgery rate in the study was 65%.

Table 1: Comparison of age between two groups (n=60).

Groups	Mean ±SD (years)	t-value	P value
A	45.200±11.589	0.935	0.354
B	42.433±11.340		

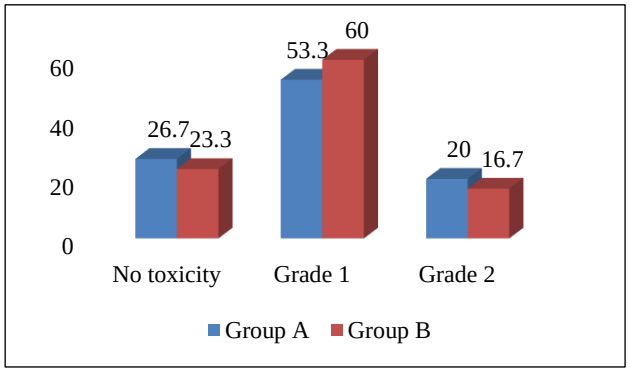

Figure 1: Column chart showed grading of tumors wise patients (n=60).

Table 2: Pre-treatment clinical stage (n=60).

Stage	A (n=30)		B (n=30)		Total (n=60)		P value
	N	%	N	%	N	%	
Stage II	7	23.3	9	30	16	26.7	0.559
Stage III	23	76.7	21	70	44	73.3	

Table 3: Treatment-related neutrophil toxicity (n=60).

Toxicity	A (n=30)		B (n=30)		Total (n=60)		P value
	N	%	N	%	N	%	
No toxicity	18	60	14	46.7	32	53.3	0.571
Grade 1	8	26.7	10	33.3	18	30	
Grade 2	4	13.3	6	20	10	16.7	

Table 4: Treatment-related gastrointestinal toxicities (n=60).

Grading	A (n=30)		B (n=30)		P value
	N	%	N	%	
Nausea					0.091
No toxicity	24	80	18	60	
Grade 1	6	20	12	40	
Vomiting					0.152
No toxicity	24	80	19	63.3	
Grade 1	6	20	11	36.7	
Diarrhea					0.086
No toxicity	10	33.3	3	10	
Grade-1	17	56.7	22	73.3	
Grade-2	3	10	5	16.7	

Table 5: Distribution of patients by gradation of hand-foot syndrome (n=60).

Syndrome	A (n=30)		B (n=30)		Total (n=60)		P value
	N	%	N	%	N	%	
No toxicity	18	60	20	66.7	38	63.3	
Grade 1	12	40	10	33.3	22	36.7	0.592

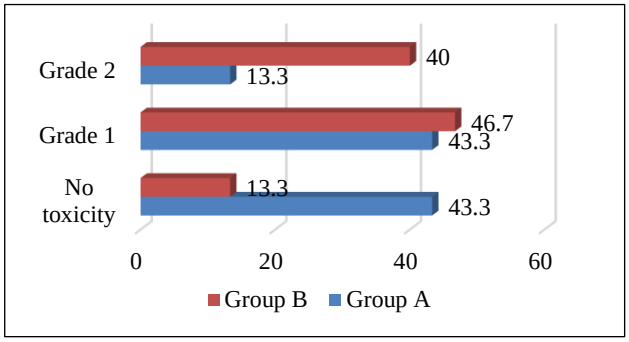

Figure 2: Distribution of the study patients by radiation-induced proctitis (n=60).

Table 6: Distribution of radiation-induced urinary toxicity (n=60).

Urinary toxicity	A (n=30)		B (n=30)		Total (n=60)		P value
	N	%	N	%	N	%	
No toxicity	14	46.7	7	23.3	21	35	0.145
Grade 1	13	43.3	17	56.7	30	50	
Grade 2	3	10	6	20	9	15	

Table 7: Distribution of tumor size after CCRT (n=60).

Tumor size	A (n=30)		B (n=30)		Total (n=60)		P value
	N	%	N	%	N	%	
T0	5	16.7	3	10	8	13.3	0.241
T1	9	30	4	13.3	13	21.7	
T2	6	20	12	40	18	30	
T3	9	30	8	26.7	17	28.3	
T4	1	3.3	3	10	4	6.7	

Table 8: Distribution of sphincter preservation (n=60).

Preser-vation	A (n=30)		B (n=30)		Total (n=60)		P value
	N	%	N	%	N	%	
Yes	22	73.3	17	56.7	39	65	0.176
No	8	26.7	13	43.3	21	35	

DISCUSSION

The present study included patients with ages ranging from 18 to 70 years, with a mean age of 45.20±11.589 years for Group A and 42.43±11.340 years for Group B. The gender distribution showed a dominance of male patients in both groups, with 56.66% in Group A and 63.3% in Group B, resulting in a total male-to-female ratio of 1.5:1. This aligns with cancer registry data indicating a male-to-female ratio of 1.4:1.[10] In this study, patients with locally advanced rectal carcinoma were enrolled, with the majority having pretreatment clinical staging at Stage III (73.3%). The distribution in Group A was 76.7%, and in Group B, it was 70.0%, with a non-significant p-value (>0.05). Among the 60 patients, 80.0% in Group A and 86.7% in Group B experienced grade-1 anemia. Grade-2 anemia was present in 10.0% of patients in Group A and 13.3% in Group B. Interestingly, 10.0% of patients in Group A did not develop any anemic condition, while in Group B, it was zero, with a non-significant p-value (>0.05). Regarding leucopenia, in Group A, 7 (23.3%) patients had grade-1, 4 (13.3%) patients had grade-2, and 19 (63.3%) patients had no leucopenia. In Group B, 10 (33.3%) patients had grade-1, 6 had grade-2, and 14 (46.7%) patients had no leucopenia. Additionally, grade-2 toxicity of neutrophil count occurred in Group A (13.3%) and in Group B (20.0%). Both groups experienced grade-1 neutropenia in 26.7% and 33.3%, and 60.0% and 46.7% of patients had no neutropenia in Group A and Group B, respectively (P>0.05). Grade-2 diarrhea occurred in 8 (13.35%) patients, and grade-1 occurred in 17 (56.7%) and 22 (73.3%) patients in Group A and B, respectively. The majority of patients in both groups had no nausea (80.0% in Group A and 60.0% in Group B) and vomiting (80.0% in Group A and 63.3% in Group B) during and after CCRT. Only 6 (20.0%) patients in Group A had grade-1 nausea and vomiting, whereas 12 (40.0%) and 11 (36.7%) patients had grade-1 nausea and vomiting, respectively, in Group B. The data were proven to be non-significant. These results are comparable with the study findings done by Hofheinz et al.[11] Grade-1 mucositis toxicity was more common in both groups (60.0% and 56.7% in Groups A and B, respectively). Grade-2 toxicity occurred in only 3.3% of both. Another important toxicity was hand-foot syndrome, which occurred mainly with fluoropyrimidine. In this study, we found that grade-1 hand-foot syndrome occurred more in Group B (40.0%) than in Group A (33.3%). Eighteen (60.0%) and 20 (63.3%) patients did not develop hand-foot syndrome. No patient had grade 2 or 3. The p-value was not significant (>0.05). Radiation also causes some toxicities. Four (13.3%) and 12 (40.0%) patients in Groups A and B developed grade-2 proctitis, whereas 13 (43.3%) and 14 (46.7%) patients developed grade-1 proctitis. Thirteen (43.3%) and 4 (13.3%) patients did not develop radiation proctitis. The result was significant (p = 0.012) and is supported by Gunnlaugsson et al.[12] Patients in both developed grade-2 dermatitis (3.3% and 10.0% in Groups A and B). Also, grade-1 dermatitis was common in both {23 (76.7%) and 24 (80.0%) patients in Group A and B, respectively}. And this result was not significant (p = 0.364). Some patients also developed grade-1 and grade-2 urinary toxicity. In Group A 13 (43.3%) patients and in Group B 17 (56.7%) patients had grade-1 urinary toxicity and 3 (10.0%) and 6 (20.0%) had grade-2 toxicity (P>0.05). These results are comparable with the study findings done by Corner et al.[13] After completing CCRT treatment, response evaluation was conducted six weeks later through clinical examination and imaging, following the predefined schedule. Complete response (CR) was observed in 5 (16.7%) patients in Group A and 3 (10.0%) patients in Group B, while partial response (PR) was noted in 22 (51.2%) patients in Group A and 21 (48.8%) in Group B. Stable disease was found in only 3 (10.0%) patients in Group A and 6 (20.0%) in Group B, with no progressive disease in either group. Statistical analysis revealed no significant difference (p = 0.467. T4-sized tumors were found in 3.3% of Group A and 10% of Group B, with a non-significant p-value (>0.05). Downsizing of tumors occurred in 25 (83.3%) patients in Group A and 22 (73.3%) in Group B, with a non-significant (P>0.05). Following the completion of CCRT and subsequent follow-up, all patients were recommended for definitive surgery. Pathological complete response was more prevalent in Group A, with 3 (10.0%) compared to 1 (3.3%) in Group B, although the p-value was non-significant (0.301). Sphincter-sparing

surgery was achieved in 22 (73.3%) patients in Group A and 17 (56.7%) in Group B. While the difference was not statistically significant (p=0.176). This finding aligns with studies by Mahmoud et al and Wagman et al.[14,15] Upon careful analysis, the present study did not demonstrate significant differences in short-term tumor responses, tumor size reduction, and sphincter-sparing surgery between 3D-CRT and 2D-RT, although 3D-CRT exhibited numerical superiority. Notably, lower gastrointestinal toxicities were more common in 2D-RT patients and were statistically significant (<0.05).

The study encounters several notable limitations. The brief duration may restrict the depth of insights gained, and the small sample size could impact clinical outcome accuracy. The non-randomized quasi-experimental design fails to address selection bias, and short-term follow-up limits comprehensive assessment. The use of drugs from different manufacturers for concurrent chemoradiotherapy introduces a potential confounding variable, affecting internal validity.

CONCLUSION

In comparing concurrent Three-Dimensional Conformal Radiotherapy (3D-CRT) and Two-Dimensional Radiotherapy (2D-RT) for patients, no statistically significant difference in tumor response was found. However, patients receiving 3D-CRT demonstrated a better response numerically. Notably, 3D-CRT showed a significant reduction in lower gastrointestinal toxicities, suggesting potential clinical benefits in terms of minimizing treatment-related complications.

Recommendations

While statistical significance in tumor response wasn't established, the observed numerical improvement and reduced toxicities emphasize the importance of considering clinical relevance and patient well-being. Further research is needed for validation and a more comprehensive understanding of these trends.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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