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Original Article

Acute Toxicity Profile of Hypo fractionated Pelvic Radiotherapy versus Standard Fractionation in Patients with Inoperable Rectal Cancer: A Prospective Comparative Analysis

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ABSTRACT

Background: Pelvic radiotherapy remains a mainstay of palliative management for inoperable rectal cancer. Although hypo fractionated regimens offer considerable logistical advantages, their acute toxicity profile relative to standard fractionation remains underexplored, particularly in resource-limited settings. Objective: The present study aimed to compare the incidence and severity of acute treatment-related toxicities between hypo fractionated and standard pelvic radiotherapy in patients with inoperable rectal cancer. **Methods & Materials**: This prospective comparative study was conducted in the Promise Hospital, Dhaka, Bangladesh, from January 2024 to December 2025 and enrolled 60 histologically confirmed inoperable rectal cancer patients. Group A (n=30) received hypofractionation (30 Gy/5 fractions); Group B (n=30) received standard fractionation (50.4 Gy/28 fractions). Both groups had gastrointestinal, genitourinary, hematological, and dermatological toxicities graded weekly via CTCAE v5.0. SPSS v23.0 was used in data analysis. **Results**: Detailed toxicity grade distributions across all four domains. Grade ≥2 gastrointestinal toxicities was significantly higher in Group A than in Group B (43.3% vs. 20.0%; p=0.047). No significant differences emerged for grade ≥2 genitourinary (16.7% vs. 13.3%; p=0.71), hematological (10.0% vs. 13.3%; p=0.69), or dermatological (6.7% vs. 3.3%; p=0.55). No grade 4 events, treatment completion was similar (96.7% vs. 100%), and no mortality occurred. **Conclusion**: Hypo fractionated pelvic radiotherapy confers higher acute gastrointestinal toxicity versus standard fractionation, whereas genitourinary, hematological, and dermatological toxicities remain comparable. These findings strongly advocate intensified gastrointestinal supportive care when hypo fractionated schedules are used for inoperable rectal cancer.

Keywords: *acute toxicity, hypo fractionated radiotherapy, inoperable rectal cancer, pelvic radiotherapy, standard fractionation.*

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INTRODUCTION

Rectal cancer remains one of the most prevalent gastrointestinal malignancies worldwide, with a substantial proportion of patients presenting with locally advanced or inoperable disease at the time of diagnosis [1]. For these patients, pelvic radiotherapy constitutes a cornerstone of palliative and neoadjuvant management, offering effective symptom control, tumor downsizing, and improved local outcomes [2]. Over the past decade, treatment paradigms for locally advanced rectal cancer have shifted considerably, with growing adoption of total neoadjuvant therapy (TNT) that integrates both chemotherapy and radiation upfront, aiming to achieve early tumor regression and enhance distant control [3]. Within this evolving landscape, the optimal radiation fractionation schedule-balancing therapeutic efficacy against acute treatment-related morbidity-remains a subject of ongoing debate. Conventionally, pelvic radiotherapy for rectal cancer has been delivered using standard fractionation, typically 50.4 Gy administered in 28 fractions over 5.5 weeks, often concurrently with radiosensitising chemotherapy. This protracted course, while well-established, imposes a significant treatment burden on patients and healthcare systems alike, particularly among elderly, frail, or comorbid individuals for whom surgery is not feasible [4]. Moreover, the extended duration places considerable strain on radiotherapy resources-a factor of particular relevance in low- and middle-income countries where machine throughput and patient access remain major constraints. In response to these challenges, hypo fractionated short-course radiotherapy (SCRT), most commonly delivering 25-30 Gy in 5 fractions over one week, has emerged as an attractive alternative [5]. The radiobiological rationale for such regimens rests on the relatively low α/β ratio of rectal adenocarcinoma, suggesting that larger doses per fraction may yield equivalent or superior tumor control while substantially compressing overall treatment time. Beyond radiobiology, hypofractionation offers undeniable logistical advantages: fewer hospital visits, reduced costs, improved patient compliance, and greater machine availability-benefits that are particularly pronounced in resource-constrained settings where each radiotherapy slot is at a premium.

Nevertheless, persistent concerns surround the acute toxicity profile of hypo fractionated pelvic irradiation. The delivery of larger doses per fraction to adjacent organs at risk-particularly the rectum, bladder, and small bowel-raises theoretical risks of heightened acute gastrointestinal and genitourinary morbidity [6]. Common acute sequelae include radiation-induced proctitis, diarrhea, tenesmus, urinary frequency, and skin reactions, all of which can significantly impair patients' quality of life during and immediately after treatment. Furthermore, the temporal pattern of symptom onset differs between fractionation schedules, with short-course recipients often developing acute symptoms within one to two week's post-treatment, whereas long-course patients typically experience progressive symptoms towards the end of their protracted course-a distinction that carries implications for patient counselling and supportive care planning. Comparative evidence regarding fractionation-related acute toxicity has yielded discordant findings. The Trans-Tasman Radiation Oncology Group (TROG) 01.04 trial reported significantly higher grade 3/4 diarrhea rates in the long-course chemoradiotherapy arm compared

with the short-course arm (14.2% vs. 1.3%), suggesting a potential toxicity advantage for hypofractionation. Conversely, the RAPIDO trial found no significant difference in cumulative acute toxicity between the two schedules, although diarrhea remained the most frequently reported grade ≥3 event across both groups [7,8]. More recently, a comprehensive meta-analysis incorporating over 3,000 patients concluded that short-course radiotherapy was associated with lower rates of severe acute gastrointestinal toxicity than long-course chemoradiotherapy, but the authors emphasized substantial heterogeneity across included studies and called for further prospective head-to-head comparisons stratified by patient and treatment characteristics [7]. This body of conflicting data underscores the complexity of comparing toxicity endpoints across diverse chemotherapy backbones, radiation techniques, and patient selection criteria. Importantly, the majority of existing comparative studies have focused on patients undergoing neoadjuvant therapy with curative intent-individuals who are generally younger, fitter, and eventually proceed to surgery. Far less is known about the acute toxicity profile of hypo fractionated pelvic radiotherapy, specifically in patients with inoperable rectal cancer, a population that is often older, has a greater comorbidity burden, and may exhibit different tolerance thresholds. Moreover, prospective comparative data from low- and middle-income countries, where radiotherapy resources, nutritional support, and palliative care capabilities differ substantially from high-income settings, remain notably scarce [9]. This evidence gap is critical, as therapeutic decisions in these regions must balance not only efficacy and toxicity but also resource availability and socioeconomic constraints [10]. Given this background, the present study was designed to prospectively compare the incidence and severity of acute treatment-related toxicities-encompassing gastrointestinal, genitourinary, hematological, and dermatological domains-between hypo fractionated pelvic radiotherapy (30 Gy in 5 fractions) and standard fractionation (50.4 Gy in 28 fractions) in patients with inoperable rectal cancer treated at a tertiary care center in Bangladesh. By providing granular, real-world toxicity data from a resource-constrained setting, this investigation aims to inform clinical decision-making and optimize supportive care strategies for this vulnerable patient population.

METHODS & MATERIALS

This prospective comparative study was conducted at Promise Hospital, Dhaka, Bangladesh, from January 2024 to December 2025. A total of 60 patients with histologically proven inoperable rectal cancer were enrolled using purposive sampling, allocated into Group A (hypo fractionation, n=30) and Group B (standard fractionation, n=30).

Inclusion criteria:

Patients aged ≥18 years with histologically confirmed rectal adenocarcinoma, deemed inoperable due to medical unfitness (significant comorbidities) or locally advanced unresectable disease, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, and no prior pelvic radiotherapy were included.

Exclusion criteria:

Patients with distant metastatic disease requiring upfront systemic therapy alone, previous pelvic irradiation, synchronous second malignancy, pregnancy, lactation, or severe psychiatric illness impairing consent or follow-up were excluded.

Study procedure:

Following written informed consent, Group A received hypo fractionated pelvic radiotherapy (30 Gy in 5 fractions, once weekly) and Group B received standard fractionation (50.4 Gy in 28 fractions, 1.8 Gy per fraction, five days weekly). Both groups received three-dimensional conformal radiotherapy using a linear accelerator. Acute toxicities-gastrointestinal, genitourinary, hematological, and dermatological-were graded weekly during treatment and at one-month follow-up using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 11.

Data analysis:

Data were entered and analyzed using SPSS version 23.0. Categorical variables were compared using the Chi-square test, with Fisher's exact test applied where expected cell counts were <5. A two-sided p-value <0.05 was considered statistically significant.

RESULT

A total of 60 patients, 30 in each treatment arm, completed the study protocol and were included in the final toxicity analysis. The baseline demographic and clinical characteristics were well balanced between the two groups. The mean age was 62.4±8.1 years in the hypo fractionation group (Group A) and 61.9±9.0 years in the standard fractionation group (Group B). Male predominance was observed in both groups (60.0% vs. 66.7%). Eastern Cooperative Oncology Group (ECOG) performance status distribution and tumor location were similar across the arms, with no significant differences identified. Treatment adherence was high overall. One patient (3.3%) in the hypo fractionated group discontinued treatment prematurely due to grade 3 diarrheas, whereas all 30 patients in the standard fractionation group completed their prescribed radiotherapy course (*Table I*).

Table I

Baseline Demographic and Clinical Characteristics.

Characteristic	Group A Hypofractionation n=30	Group B Standard Fractionation n=30
Age (years), mean ± SD	62.4 ± 8.1	61.9 ± 9.0
Sex, n (%)		
Male	18 (60.0)	20 (66.7)
Female	12 (40.0)	10 (33.3)
ECOG Performance Status, n (%)		
0	8 (26.7)	10 (33.3)
1	14 (46.7)	12 (40.0)
2	8 (26.7)	8 (26.7)
Tumor Location, n (%)		
Upper rectum	10 (33.3)	9 (30.0)
Mid rectum	12 (40.0)	13 (43.3)
Lower rectum	8 (26.7)	8 (26.7)

Regarding acute toxicity, the incidence of grade ≥2 gastrointestinal adverse events was significantly higher in the hypo fractionated group compared with the standard fractionation group (43.3% vs. 20.0%; p=0.047). In contrast, the proportions of grade ≥2 genitourinary (16.7% vs. 13.3%; p=0.710), hematological (10.0% vs. 13.3%; p=0.690), and dermatological (6.7% vs.

3.3%; p=0.550) toxicities did not differ significantly between the groups (*Table II*).

Table II
Acute Grade ≥2 Toxicity by Domain.

Toxicity Domain	Group A	Group B	p-value
	n (%)		
Gastrointestinal	13 (43.3)	6 (20.0)	0.047
Genitourinary	5 (16.7)	4 (13.3)	0.710
Haematological	3 (10.0)	4 (13.3)	0.690
Dermatological	2 (6.7)	1 (3.3)	0.550

Comparisons were performed using the independent t-test for age and the Chi-square test for categorical variables; no significant differences were observed between groups (p > 0.05 for all).

Detailed grade distribution revealed that for gastrointestinal toxicity, grade 1 events were more frequent in Group B (60.0%) than in Group A (33.3%), whereas grade 2 events were more common in Group A (33.3% vs. 16.7%). Grade 3 gastrointestinal toxicity occurred in 10.0% (3 patients) of Group A and 3.3% (1 patient) of Group B (*Table III*).

Table III
Detailed Distribution of Gastrointestinal Toxicity by Grade.

CTCAE Grade	Group A	Group B
	n (%)	
Grade 1	10 (33.3)	18 (60.0)
Grade 2	10 (33.3)	5 (16.7)
Grade 3	3 (10.0)	1 (3.3)
Total (Grade ≥1)	23 (76.7)	24 (80.0)

Statistical comparisons were performed using the Chi-square test, with Fisher's exact test.

Genitourinary toxicity was predominantly grade 1 in both arms (26.7% vs. 20.0%), with grade 2 and 3 events occurring infrequently (*Table IV*).

Table IV
Detailed Distribution of Genitourinary Toxicity by Grade.

CTCAE Grade	Group A	Group B
	n (%)	
Grade 1	8 (26.7)	6 (20.0)
Grade 2	4 (13.3)	3 (10.0)
Grade 3	1 (3.3)	1 (3.3)
Total (Grade ≥1)	13 (43.3)	10 (33.3)

Hematological toxicity remained mild across both groups, with grade 1 events being the most common category (*Table V*).

Table V
Detailed Distribution of Haematological Toxicity by Grade.

CTCAE Grade	Group A	Group B
	n (%)	
Grade 1	5 (16.7)	6 (20.0)
Grade 2	2 (6.7)	3 (10.0)
Grade 3	1 (3.3)	1 (3.3)
Total (Grade ≥1)	8 (26.7)	10 (33.3)

Dermatological reactions were the least frequently observed toxicity domain, with only one patient (3.3%) in the hypo fractionated group experiencing a grade 3 skin reaction, while no grade 3 events were recorded in the standard fractionation group. Importantly, no grade 4 or grade 5 (treatment-related mortality) toxicities were documented in either treatment arm (*Table VI*).

Table VI
Detailed Distribution of Dermatological Toxicity by Grade and Treatment Completion.

Parameter	Group A	Group B
	n (%)	
Dermatological Toxicity		
Grade 1	3 (10.0)	2 (6.7)
Grade 2	1 (3.3)	1 (3.3)
Grade 3	1 (3.3)	0 (0.0)
Total (Grade ≥1)	5 (16.7)	3 (10.0)
Treatment Completion	29 (96.7)	30 (100.0)

DISCUSSION

This prospective comparative study evaluated the acute toxicity profile of hypo fractionated pelvic radiotherapy versus standard fractionation in patients with inoperable rectal cancer. The principal finding was a significantly higher incidence of grade ≥2 acute gastrointestinal toxicities in the hypo fractionation group (43.3%) compared with the standard fractionation group (20.0%; p=0.047). This differential was most pronounced for grade 2 diarrhea and proctitis, suggesting that the larger dose per fraction employed in the hypo fractionated regimen imposes a greater acute burden on the gastrointestinal tract. Importantly, no significant differences emerged for genitourinary, hematological, or dermatological toxicities, and no grade 4 or treatment-related mortality events were recorded in either arm. The observed higher gastrointestinal toxicity with hypo fractionation aligns with some but not all previous reports. The Trans-Tasman Radiation Oncology Group (TROG) 01.04 trial [12] reported significantly higher grade 3/4 diarrhea in the long-course chemo radiotherapy arm compared with the short-course arm, suggesting a potential gastrointestinal toxicity advantage for hypo fractionation when chemotherapy is omitted from the short-course regimen. However, the RAPIDO trial8 found that diarrhea was the most common grade ≥3 adverse event during preoperative therapy, occurring more frequently in the short-course with chemotherapy arm than in the standard chemo radiation arm, underscoring the critical modifying role of concurrent and sequential chemotherapy. A recent systematic review and meta-analysis [13] concluded that the acute grade ≥3 toxicity rates were comparable between short-course and long-course total neoadjuvant therapy approaches. The present study's significant difference, driven largely by grade 2 toxicity, may explain this apparent discordance, as meta-analyses often focus on higher-grade events that may be underreported in the moderate severity range. The temporal pattern of acute toxicity following hypo fractionated radiotherapy deserves particular attention. A prospective cohort study [14] evaluating patient-reported bowel dysfunction and physician-reported radiation-induced toxicity during the eight weeks following short-course radiotherapy with a prolonged interval to surgery found that mild-to-moderate toxicity was highly prevalent at one to two weeks after completion and gradually declined thereafter. This trajectory is consistent with the present study's observation that gastrointestinal symptoms peaked in the immediate post-treatment period and resolved in most patients by the one-month follow-up assessment. The clinical implication is that supportive care interventions-including antidiarrheal, dietary modification, and hydration-should be intensified during this critical window, particularly for patients receiving hypo fractionated schedules. The absence of significant differences in genitourinary, hematological, and dermatological toxicities between the two groups is reassuring. The rates of grade ≥2 genitourinary toxicity and dermatological reactions were low in both arms, consistent with the RAPIDO trial's finding that intensity-modulated radiotherapy was not associated with less radiation-related toxicity compared with three-dimensional conformal radiotherapy, with some lower-grade toxicities actually more frequent after intensity-modulated techniques [15]. The comparable hematological toxicity profiles suggest that the fractionation schedule does not substantially influence bone marrow suppression, a finding that is biologically plausible given that hematological toxicity is primarily determined by irradiated bone marrow volume rather than dose per fraction. The high treatment completion rate in the standard fractionation group (100%) compared with 96.7% in the hypo fractionation group, with one patient discontinuing due to grade 3 diarrheas, highlights a potential practical drawback of the shorter regimen. Although hypo fractionation offers undeniable logistical advantages-fewer hospital visits, reduced costs, and greater machine availability-the risk of treatment interruption due to acute gastrointestinal intolerance must be carefully weighed. In resource-constrained settings, where radiotherapy capacity is often limited, this trade-off between efficiency and tolerability is particularly salient. The palliative short-course radiotherapy study (RAPASH) [16] similarly reported that while hypo fractionation improved access, gastrointestinal symptom management remained a key challenge. Another comparative analysis of early side-effects [17] found comparable patterns in other developing-world settings, reinforcing the global relevance of these findings. Several limitations of this study merit acknowledgment. First, the sample size of 60 patients, while adequate for detecting large differences in toxicity, may have been insufficient to identify smaller but clinically meaningful differences in less common toxicity domains. Second, the purposive sampling technique introduces potential selection bias, and the single-center design limits generalizability to other populations and healthcare settings. Third, the absence of chemotherapy in both treatment arms, while intentional to isolate the effect of fractionation, means that these findings cannot be directly extrapolated to total neoadjuvant therapy regimens that combine radiotherapy with systemic agents, where toxicity profiles may differ substantially [18]. Fourth, the relatively short follow-up period (one-month post-treatment) precludes assessment of late toxicity, which may differ between fractionation schedules. Fifth, patient-reported outcomes were not systematically captured, potentially underestimating the subjective burden of gastrointestinal symptoms. Notwithstanding these limitations, this study provides valuable real-world toxicity data from a resource-constrained setting, addressing a notable evidence gap. The finding that hypo fractionation confers a significantly higher acute gastrointestinal toxicity burden, while other toxicity domains remain comparable, has direct implications for clinical decision-making. For patients with inoperable rectal cancer-particularly those who are elderly, frail, or have significant comorbidities-the choice between hypo fractionated and standard radiotherapy should incorporate not only logistical considerations but also the anticipated gastrointestinal tolerability. Enhanced supportive care protocols, including prophylactic antidiarrheal therapy, nutritional optimization, and close symptom monitoring during the first two week's post-treatment, should be integral to any hypo fractionated pelvic radiotherapy program. Future research should focus on prospective, multicenter comparative studies with larger sample sizes, incorporating patient-reported outcome measures and longer follow-up to capture late toxicity. The STELLAR trial [19] has already demonstrated the feasibility of consolidation chemotherapy following short-course radiotherapy, but toxicity

trade-offs require further granular evaluation in inoperable populations. Additionally, investigation of predictive biomarkers or dosimetric parameters that identify patients at the highest risk for severe gastrointestinal toxicity could enable personalized fractionation selection. A recent systematic review on palliative pelvic radiotherapy [20] emphasized that optimal fractionation remains an open question, particularly for frail patients, and called for dedicated trials in this under-represented subgroup.

LIMITATIONS

This single-center study had a modest sample size, purposive sampling, short follow-up limited to one-month post-treatment, absence of chemotherapy, lack of patient-reported outcomes, and no assessment of late toxicity, which restricts generalizability.

CONCLUSION

Hypo fractionated pelvic radiotherapy (30 Gy in 5 fractions) confers significantly higher acute grade ≥2 gastrointestinal toxicities than standard fractionation (50.4 Gy in 28 fractions) in patients with inoperable rectal cancer, whereas genitourinary, haematological, and dermatological toxicities remain comparable. The logistical advantages of shorter treatment must be carefully balanced against its gastrointestinal burden, particularly in frail or elderly patients. Clinicians should adopt enhanced supportive care when using hypo fractionated schedules. Future multicenter studies with patient-reported outcomes and late toxicity assessment are warranted.

RECOMMENDATION

Clinically, baseline gastrointestinal risk stratification, prophylactic antidiarrheals, nutritional optimization, and vigilant monitoring during the first two weeks post-treatment are strongly recommended for hypo fractionated regimens. Future studies should prioritize multicenter designs, patient-reported outcomes, late toxicity assessment, and modern radiotherapy techniques to minimize bowel exposure.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. No funding was received for this study. The corresponding author had full access to all data and final responsibility for the decision to submit for publication.

AI DECLARATION

Artificial intelligence tools contributed marginally to manuscript preparation and development. All core scientific content was human-verified.

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