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Acute Toxicity Comparison between 3DCRT and SIB-IMRT in Preoperative Concurrent Chemo-Radiotherapy for Locally Advanced Rectal Cancer

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Abstract

This study was conducted with the primary objective of evaluating and contrasting the acute toxicity outcomes associated with two radiotherapy modalities—3D-CRT and SIB-IMRT—administered in the preoperative setting for patients diagnosed with locally advanced rectal cancer (LARC). A total of 40 individuals who met the diagnostic criteria for LARC were enrolled and randomly allocated into two equal cohorts. Group A underwent 3D-CRT in combination with concurrent capecitabine, while group B received SIB-IMRT, also paired with capecitabine, as part of their neoadjuvant regimen. During the combined chemo-radiotherapy treatment, patients were evaluated weekly, and any instances of acute toxicity were documented. A significant reduction in grade 3 genitourinary toxicities was observed in group B compared to group A, which was statistically significant with a P-value of 0.048. Additionally, when analyzing gastrointestinal toxicities, both grade 2 and grade 3 adverse events were significantly more prevalent in the 3D-CRT cohort compared to those receiving SIB-IMRT, with P-values of 0.043 and 0.021, respectively. Dosimetric comparisons showed no significant changes in D_{mean} or D_{max} values for the urinary bladder (UB) and small bowel (SB) between the two treatment techniques. However, the V45—the volume that receives at least 45 Gy—of the UB was significantly higher in patients treated with 3D-CRT compared to those receiving SIB-IMRT (P = 0.003), and a similar trend was observed for the SB (P = 0.001). Overall, the reduced V45 exposure for both UB and SB in the SIB-IMRT group appeared to correlate with the improved toxicity profile, as the frequency of grade 2 genitourinary and both grade 2 and grade 3 gastrointestinal toxicities were significantly lower in this cohort relative to the 3D-CRT group.

Keywords: Gastrointestinal toxicities, 3DCRT, SIB-IMRT, Genitourinary

Introduction

The standard therapeutic strategy for managing locally advanced rectal cancer (LARC), particularly in cases exhibiting extra-peritoneal involvement, typically involves neoadjuvant radiotherapy (RT), either as a standalone approach or combined with chemotherapy (CT) [1–3]. For patients presenting with unresectable tumors or in scenarios necessitating tumor down-sizing or down-staging—such as cT3 tumors adjacent to the mesorectal fascia (MRF) with or without nodal involvement (N0) in the lower rectum, or more extensive disease categorized as cT3–4 with MRF+/N0–2—employing multimodal therapy is generally favored [4]. In designing the radiotherapy fields for LARC, it is essential to encompass not only the primary lesion but also the entire mesorectum, the pre-sacral region and involved regional lymphatics. Historically, 2D RT techniques using three or four fields were employed to cover this anatomical area. The advent of 3D-CRT (three-dimensional conformal radiotherapy) has led to improvements in dose distribution to the target while offering better sparing of organs at risk (OARs) [5]. However, due to the complex, horseshoe-like geometry of the target volume that closely surrounds structures like the bladder and small bowel in patients with rectal

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adenocarcinoma, achieving optimal OAR sparing with 3D-CRT has proven challenging [6].

To address these limitations, more sophisticated technologies such as intensity-modulated radiotherapy (IMRT) have been introduced, offering enhanced precision in limiting unnecessary radiation exposure to adjacent critical organs. A particular advancement, known as simultaneous integrated boost IMRT (SIB-IMRT), enables differential dosing within a single treatment session by escalating the dose to specific high-risk regions while maintaining minimal exposure to elective areas. This technique confers both dosimetric and clinical benefits, enhancing therapeutic effectiveness while reducing toxicity [6, 7].

There is a well-established correlation between radiation exposure to the small bowel and the development of acute diarrhea during preoperative chemoradiation in rectal cancer patients [8]. Numerous dosimetric investigations have affirmed that IMRT allows for superior dose conformity and target coverage while decreasing the radiation burden on adjacent OARs [9, 10]. Furthermore, several retrospective analyses have shown that IMRT can significantly reduce treatment-related toxicities, minimize the occurrence of therapy interruptions, and lower the likelihood of patient hospitalization during treatment [11–14].

Given this background, the current study was undertaken to examine and compare the acute toxicity profiles of patients treated with either 3D-CRT or SIB-IMRT, along with evaluating the extent of radiation exposure to OARs associated with each modality.

Materials and Methods

Before initiating therapy, comprehensive verbal and written explanations regarding the study protocol were given to all participants. Enrolment was contingent upon each patient's provision of written informed consent. Additionally, ethical clearance and protocol approval were secured from the local institutional review board and research ethics committee under approval number N-130-2022.

Study framework and eligibility criteria

This prospective investigation was conducted at the Clinical Oncology Department of Kasr El Ainy, Cairo University, spanning from September 2022 through February 2023. A total of 40 individuals diagnosed with locally advanced rectal cancer (LARC) were included and randomly assigned into two equal cohorts. Group A was administered preoperative 3D-CRT in combination with capecitabine, whereas group B underwent preoperative SIB-IMRT, also paired with capecitabine as concurrent chemotherapy.

To qualify for participation, patients were required to have a histologically verified diagnosis of rectal adenocarcinoma, classified as clinical stage II or III. Baseline evaluations comprised a comprehensive set of diagnostic tools, including a dedicated rectal MRI, CT scans of the chest, abdomen, and pelvis, as well as proctoscopy or endorectal ultrasound, supported by physical assessment and standard laboratory investigations.

Treatment protocol

- *Radiotherapy*

Simulation for radiotherapy planning was carried out using a CT scan with 3 mm slice intervals, encompassing all relevant anatomical areas. Patients assigned to the 3D-CRT arm were positioned prone during planning and treatment, while those receiving IMRT were placed supine. To optimize bladder filling and maintain consistency in organ position, all participants were instructed to consume a designated amount of fluid and refrain from voiding urine for one hour before the simulation and before each treatment session. Treatment planning adhered to international standards as outlined in ICRU reports 50, 62, and 83 [15, 16].

The gross tumor volume (GTV) included all radiologically visible tumors and any enlarged lymph nodes. A margin of 1 cm around the GTV formed the clinical target volume 2 (CTV2), designated for dose escalation, while CTV1 encompassed CTV2, the mesorectal fat, and relevant lymphatic drainage pathways from the L5/S1 vertebral junction to 4 cm below the tumor's inferior border. In cases involving invasion of the genitourinary tract, the external iliac lymph nodes were included. If the levator ani muscle was infiltrated, the ischiorectal fossa was also contoured. An additional margin of 5 to 10 mm was added to the clinical volumes to account for daily anatomical variation, such as changes in bowel gas or bladder filling. A further 5 mm expansion produced the final planning target volumes (PTV1 and PTV2).

In the 3D-CRT group, treatment planning was executed using either a 3-field or 4-field box technique. A total of 45 Gy was administered in 25 fractions over 5 weeks to PTV1, followed by a localized boost of 5.4 Gy in 3

fractions targeting PTV2, culminating in a total of 50.4 Gy. In contrast, SIB-IMRT plans utilized 7 to 9 beam angles delivered through a dynamic multileaf collimator system. The prescribed doses were 45 Gy in 25 fractions to PTV1 and 50 Gy in 25 fractions to PTV2, delivered simultaneously over 5 weeks. Treatments for both arms were conducted on a Clinac 2100 linear accelerator (Varian, Palo Alto, USA) using 6 MV photon energy.

For SIB-IMRT, particular attention was given to ensuring a steep dose gradient outside the PTVs, reducing radiation exposure to adjacent healthy tissues. The maximum dose (D_{max}) delivered to the bladder and small bowel outside PTV1 and PTV2 was planned to remain below the prescribed limits. Weekly position verification was performed using an electronic portal imaging device (EPID) to ensure accurate patient alignment throughout treatment.

Dose constraints for organs at risk were strictly followed: for the small bowel, D_{max} was set to remain under 55 Gy, and the volume receiving 45 Gy (V45Gy) was limited to less than 195 cc. For the bladder, the constraint was V35Gy under 35% and V30Gy below 50% [17, 18].

Following the completion of chemoradiotherapy, all patients from both treatment groups (arm A and arm B) were scheduled for surgical resection within a window of 6 to 8 weeks.

• *Chemotherapy*

Throughout the radiotherapy course, patients in both arms (arm A and arm B) received concurrent chemotherapy consisting of Capecitabine administered orally at a dose of 825 mg/m² twice daily, with one of the doses scheduled to be taken approximately one hour before each radiotherapy session. No doses were given during weekends.

• *Acute toxicity assessment*

Participants underwent weekly clinical evaluations during chemoradiotherapy. During each visit, any acute side effects were documented. The assessment of acute toxicities and adherence to the treatment regimen was performed weekly following the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [19].

Statistics

Comparative analysis of patient demographics, treatment features, and commonly observed toxicities between the 3D-CRT and IMRT groups was conducted using Fisher's exact test for categorical variables and t-tests for continuous variables. Statistical significance was determined at a threshold of $P \leq 0.05$. All statistical modeling and hypothesis testing were performed using R software, version 3.13 [20].

Results and Discussion

Patient, treatment, and tumor characteristics

From September 2022 through February 2023, a total of 40 individuals diagnosed with locally advanced rectal cancer (LARC) received treatment at the Kasr Al-Ainy Center of Clinical Oncology (NEMROCK). These patients were randomly assigned into two equal groups: arm A was managed with preoperative 3D-CRT plus capecitabine, whereas arm B underwent preoperative SIB-IMRT in combination with capecitabine. Detailed baseline data regarding the clinical, pathological, and therapeutic characteristics of all participants are summarized in **Table 1**.

Table 1. The patient and tumoral characteristics of both arms involved in the study

Characteristic	Arm A % (n = 20) 3D-CRT	Arm B % (n = 20) IMRT	P-value
Gender			
Male	15 (75%)	14 (70%)	4.45
Female	5 (25%)	6 (30%)	
Age (years), median	60 (56-64)	61 (57-65)	0.14
ECOG performance status			
0	6 (30%)	5 (25%)	0.62
1	12 (60%)	14 (70%)	
2	2 (10%)	1 (5%)	
Tumor grade			
Well-differentiated	2 (10%)	2 (10%)	0.72

Moderately differentiated	12 (60%)	10 (50%)	
Poorly differentiated	4 (20%)	4 (20%)	
Unknown	2 (10%)	2 (10%)	
Clinical Stage at diagnosis			
II	10 (50%)	9 (45%)	0.62
III	10 (50%)	11 (55%)	
cT-stage			
cT2	5 (25%)	4 (20%)	0.52
cT3	14 (70%)	13 (65%)	
cT4	1 (5%)	3 (15%)	
cN-stage			
N0	2 (10%)	3 (15%)	0.32
N1	14 (70%)	10 (50%)	
N2	4 (20%)	7 (35%)	
Mesorectum			
Involved	12 (60%)	13 (65%)	0.43
Not involved	8 (40%)	7 (35%)	
Distance from the anal verge (cm)			
< 5 cm	11 (55%)	8 (40%)	0.23
> 5 cm	9 (45%)	12 (60%)	
Interrupted radiotherapy course			
Yes	2 (10%)	1 (5%)	0.53
No	18 (90%)	19 (95%)	

The demographic and clinical profiles, including age, sex, and performance status, were comparably distributed between both treatment arms, indicating no initial imbalance. The histological grading revealed that moderately differentiated adenocarcinoma was the most frequent in both arms, occurring in 60% of patients receiving 3D-CRT (arm A) and 50% of those undergoing SIB-IMRT (arm B). Concerning clinical staging, stage II disease accounted for half of the cases in arm A, whereas 45% of arm B fell under this category, though the difference was not statistically meaningful. Additionally, mesorectal involvement was seen in 60% of arm A patients compared to 65% in arm B, again lacking statistical significance. Disruption or delay in radiation therapy schedules showed no remarkable disparity between the two techniques, with a P-value of 0.53 supporting this similarity.

Assessment of early treatment-related toxicities

The incidence of acute side effects during treatment varied between the groups and is outlined in **Table 2**. While mild genitourinary symptoms (grade 1) appeared more often among SIB-IMRT recipients (arm B), this trend did not achieve statistical weight. Notably, however, severe genitourinary toxicity (grade 3) was significantly less prevalent in arm B than in arm A, with a P-value of 0.048 confirming this difference.

When evaluating gastrointestinal adverse effects, 80% of individuals in arm B reported mild symptoms (grade 1), a significantly higher frequency compared to those treated in arm A (P = 0.032). Conversely, moderate to severe GI toxicities (grades 2 and 3) were considerably more pronounced among arm A patients, with P-values of 0.043 and 0.021, respectively, indicating meaningful distinctions.

No significant variation was noted across the two cohorts in terms of hematologic complications, skin-related toxicities, or cardiac side effects. Similarly, acute leakage post-treatment was observed in three patients from arm A and two patients from arm B, with this difference lacking statistical relevance.

Table 2. Theradiotherapy-induced adverse events were encountered during the treatment course in both arms

Adverse event	Arm A % (n = 20) 3D-CRT	Arm B % (n = 20) IMRT	P-value
Genito-urinary			

G0	1 (5%)	1 (5%)	1.000
G1	11 (55%)	13 (65%)	0.083
G2	4 (20%)	4 (20%)	1.000
G3	4 (20%)	2 (10%)	0.048
Gastro-intestinal			
G0	0 (0%)	`0 (0%)	1.000
G1	10 (50%)	16 (80%)	0.032
G2	7 (35%)	4 (20%)	0.043
G3	3 (15%)	0 (0%)	0.021
Hematological			
G0	5 (25%)	4 (20%)	0.073
G1	13 (65%)	14 (70%)	0.082
G2	2 (10%)	2 (10%)	1.000
G3	0 (0%)	0 (0%)	1.000
Skin			
G0	1 (5%)	1 (5%)	1.000
G1	15 (75%)	12 (60%)	0.062
G2	4 (20%)	7 (35%)	0.071
G3	0 (0%)	0 (0%)	1.000
Cardiac			
G0	17 (85%)	19 (95%)	0.093
G1	3 (15%)	1 (5%)	0.061
G2	0 (0%)	0 (0%)	1.000
G3	0 (0%)	0 (0%)	1.000
Early leakage			
Absent	17 (85%)	18 (90%)	0.076
Present	3 (15%)	2 (10%)	0.092

Organ-at-Risk dose analysis

Representative images illustrating three-dimensional dose distributions for both treatment strategies are presented in **Figures 1 and 2**, highlighting the spatial coverage achieved using 3D-CRT and SIB-IMRT, respectively. A comparative dose-volume histogram (DVH) analysis, depicted in **Figure 3**, offers a side-by-side evaluation of PTV coverage and dose exposure to organs at risk (OARs) under each planning modality.

The urinary bladder and small bowel were the principal OARs investigated in this study. For the urinary bladder, analysis revealed no significant variation between the two radiotherapy techniques in terms of both Dmean and Dmax, with p-values of 0.521 and 0.362, respectively. However, a notable difference was observed in the V45 parameter, which was substantially greater in the 3D-CRT cohort compared to SIB-IMRT, a finding supported by a statistically significant p-value of 0.003.

Turning to the small bowel, comparisons of the maximum and mean doses also indicated no significant differences, reflected by P-values of 0.378 and 0.324, respectively. Nevertheless, the V45 dose metric once again favored SIB-IMRT, with 3D-CRT plans delivering a significantly higher volume, as demonstrated by a P-value of 0.001.

Further quantitative details and intergroup comparisons of the bladder and small bowel dosimetric parameters are systematically compiled in **Table 3**.

Table 3. Comparison of dose-volume parameters of the bladder and small bowel between the SIB-IMRT and 3D-CRT

Organ	Parameter	3D-CRT plan	SIB-IMRT plan	P-value
Bladder	D_{mean} (Gy)	34.3 ± 35.5	33.5 ± 5.2	0.521
	D_{max} (Gy)	48.2 ± 2.3	48.8 ± 5.1	0.362
	V15 (cm^3)	115.4 ± 100.5	138.5 ± 98.1	0.254
	V45 (cm^3)	31.4 ± 35.4	16.8 ± 17.1	0.003

Small bowel	D_{mean} (Gy)	24.5 ± 7.1	25.6 ± 8.4	0.378
	D_{max} (Gy)	45.1± 9.2	42.9 ± 13.7	0.324
	V15 (cm^3)	170 ± 158.6	220 ± 140.5	0.118
	V45 (cm^3)	37.8 ± 44.1	9.5 ± 10.2	0.001

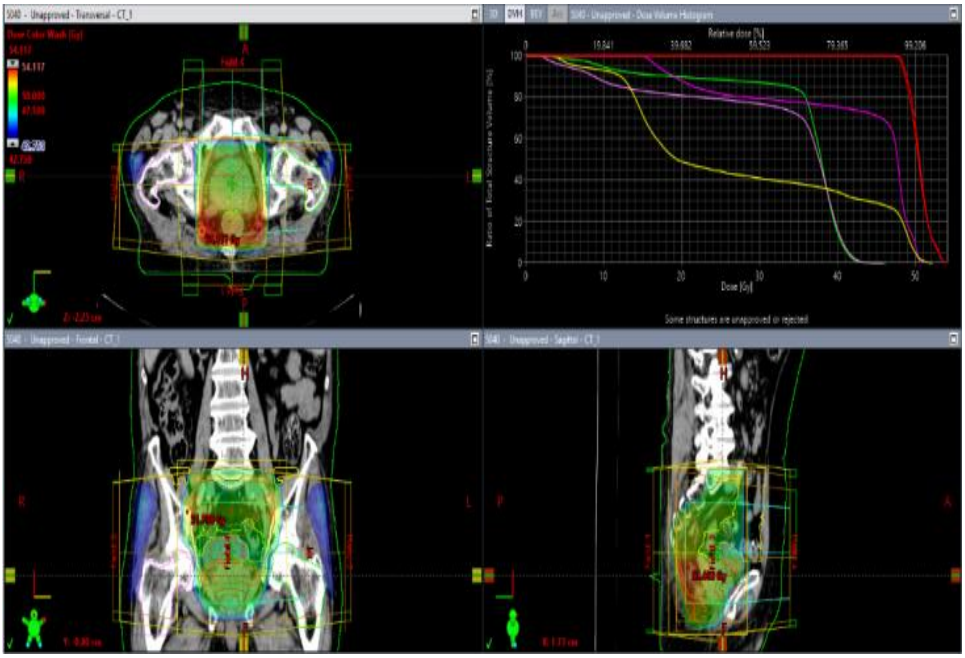

Figure 1. Dose distribution in 3D view for the 3D-CRT plan

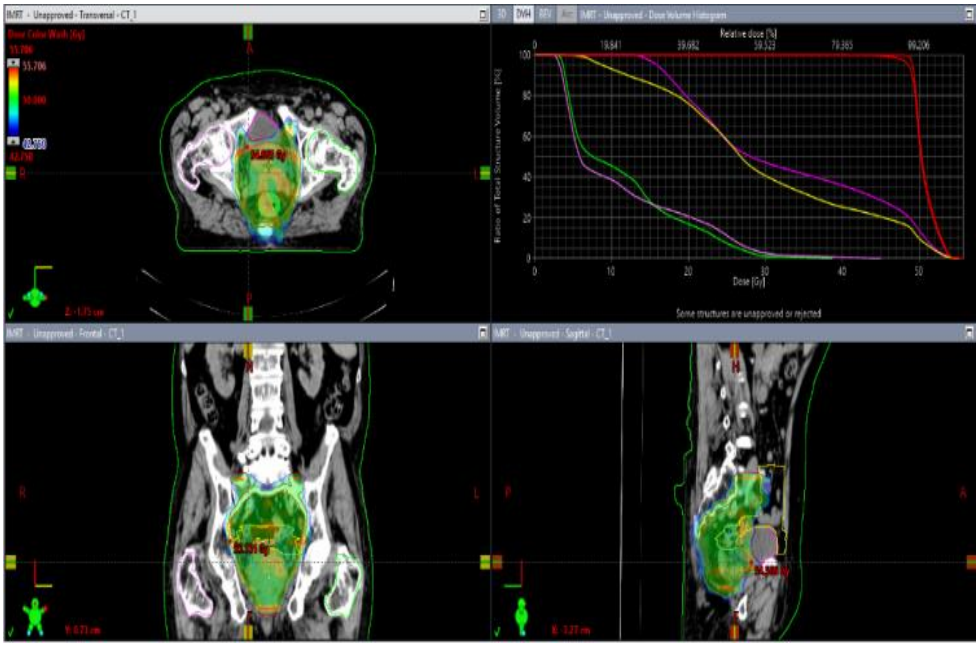

Figure 2. Dose distribution in 3D view for the SIB-IMRT plan

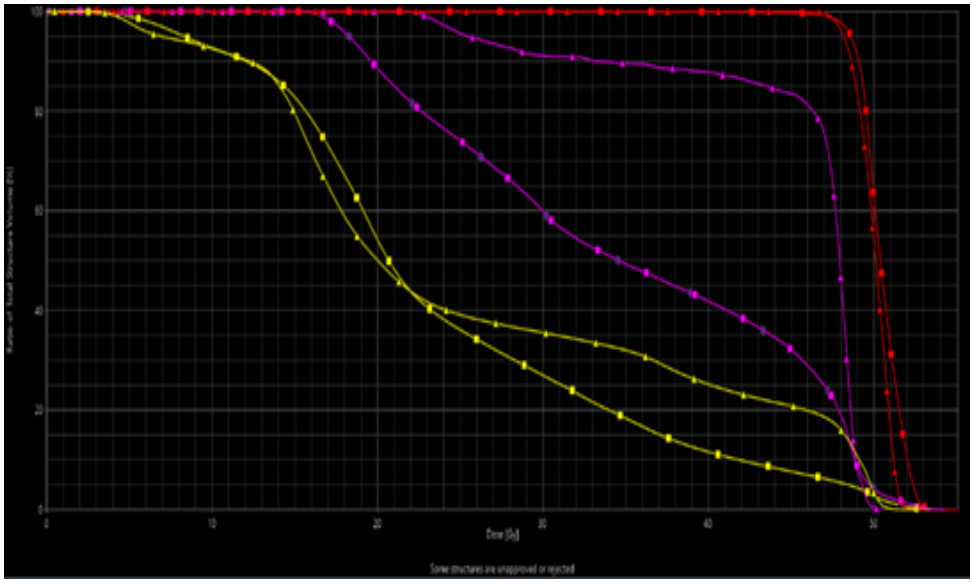

Figure 3. A comparative DVHs for PTV coverage and doses to OAR for 3D-CRT (triangles) and SIB-IMRT (squares)

Our results align with findings from various dosimetric and clinical studies indicating that IMRT results in lower doses to the small bowel, leading to decreased gastrointestinal toxicity. A dosimetric study conducted by Yang *et al.* [14] observed that women undergoing CCRT for rectal cancer experienced higher rates of grade 2 diarrhea, starting at week four of treatment (24% in women vs. 11% in men, P = 0.01). Furthermore, patients who underwent 3D-CRT had higher incidences of grade 2 diarrhea than those treated with IMRT (22% vs. 12%, respectively, P = 0.03) [14]. A retrospective study from the Mayo Clinic found that patients receiving IMRT had a significantly lower frequency of grade 2 gastrointestinal diarrhea compared to those treated with 3D-CRT (23% for IMRT vs. 48% for 3D-CRT) [13]. Conversely, there was no significant difference in the incidence of proctitis or urinary toxicity between the two treatment groups. Parekh *et al.* [12] reported that 3D-CRT resulted in significantly higher grade 2 gastrointestinal diarrhea compared to IMRT (43% vs. 10%, p = 0.014), although no grade 3 or higher diarrhea was seen in the IMRT group, likely due to the study's small sample size.

In a study by Jabbour *et al.* [11], IMRT demonstrated a substantial reduction in grade 3 toxicities, including pain, fatigue, and hematological, genitourinary, and gastrointestinal symptoms. While gastrointestinal symptoms weren't significantly reduced in isolation, patients receiving combined concurrent chemotherapy had more grade 3 toxicities than those on single-agent chemotherapy (43% vs. 11%, P = 0.009). Additionally, IMRT patients experienced fewer hospitalizations and emergency room admissions (2% vs. 14% for 3D-CRT, P = 0.005).

A large retrospective analysis by Ng *et al.* [21] also evaluated acute toxicities in rectal adenocarcinoma patients treated with either IMRT or 3D-CRT. This study, which included preoperative primary tumors and single-agent 5-fluorouracil chemotherapy, found that IMRT significantly reduced grade 2 diarrhea and genitourinary toxicity, with a slight trend toward reducing proctitis. Younger patients (under 55) were more likely to experience severe proctitis, highlighting the benefits of IMRT for minimizing these acute toxicities in this age group.

In terms of organ-at-risk (OAR) doses, our findings mirror those of other studies that highlight IMRT's superior ability to spare OARs from high doses. A dosimetric study by Arbea *et al*. [9] comparing IMRT to 3D-CRT for LARC patients revealed that IMRT offered a distinct advantage, particularly in protecting the bladder. The volume of the bladder receiving ≥ 40 Gy was nearly one-third less in the IMRT group compared to the 3D-CRT group (34.4 cc vs. 94.7 cc, $p < 0.05$). Similarly, the volume of the small bowel receiving ≥ 40 Gy was significantly lower with IMRT (68.9 cc vs. 178.3 cc, $P < 0.05$) [9]. Another study by Duthoy *et al.* [22] comparing IMAT with 3D-CRT in LARC patients found

that IMAT delivered significantly lower doses to the small bowel. A small retrospective study by Guerrero *et al*. demonstrated that IMRT reduced the volume of the small bowel receiving 45 Gy and 50 Gy when compared to 3D-CRT [23]. Lastly, Tho *et al*. [8] found that IMRT inverse planning resulted in a reduction of median small bowel dose by 5.1 Gy (P = 0.008) when compared to 3D-CRT.

Conclusion

Several dosimetric studies have highlighted the advantage of IMRT in reducing the radiation dose to organs at risk (OARs), particularly the small bowel, which leads to a reduction in the incidence of diarrhea. Our results support these findings, showing that the V45 dose was significantly lower in the IMRT treatment plans compared to 3D-CRT. This dose reduction was associated with a lower frequency of grade 2 genitourinary and grade 2 and 3 gastrointestinal toxicities in the IMRT group when compared to the 3D-CRT group.

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