Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/zdgmwd88

SHORT VS LONG COURSE RADIOTHERAPY IN RECTAL CANCER: ACUTE TOXICITY AND OUTCOMES FROM A SINGLE-CENTRE COHORT"

Viraj Modi[1], Nikhil Bathija[2*], Ankita Parikh[3], Jayesh Kumar Singh[4], Vinay Shivhare[5], Satyajit Rath[6]

[1]Consultant Radiation Oncologist, Shankus Cancer Hospital, Himmatnagar, Gujarat.
[2*]Senior Resident, Department of Radiation Oncology, All India Institute of Medical Sciences (AIIMS) Bathinda, Punjab
[3]Professor & Head, Department of Radiation Oncology, The Gujarat Cancer & Research Institute (GCRI), Ahmedabad
[4]Assistant Professor, Department of Radiation Oncology, The Gujarat Cancer & Research Institute (GCRI), Ahmedabad
[5]Associate Professor, Department of Radiation Oncology, The Gujarat Cancer & Research Institute (GCRI), Ahmedabad
[6]Associate Professor, Department of Radiation Oncology, All India Institute of Medical Sciences (AIIMS) Rajkot, Gujarat.

***Corresponding Author:** Dr. Nikhil Bathija
*(MD, PDF)- Senior Resident, Department of Radiation Oncology, All India Institute of Medical Sciences (AIIMS), Bathinda, Punjab. Email: drnikhiloncology@gmail.com

Abstract

Background: Short-course radiotherapy (SCRT) and long-course chemoradiation (LCRT) are accepted neoadjuvant options in locally advanced rectal cancer (LARC), yet real-world comparative data on acute toxicity and early surgical quality are limited.

Methods: This single-centre randomized two-arm cohort compared SCRT (25 Gy/5 fractions with delayed surgery) versus LCRT (45 Gy/25 fractions with concurrent capecitabine plus 5.4 Gy boost). Acute toxicities were graded by RTOG/WHO criteria. The primary endpoint was clinically relevant acute toxicity; secondary endpoints included sphincter preservation, margin status, postoperative complications, pathological response, and early distant metastasis. Analyses were intention-to-treat using Fisher's exact tests with 95% CIs.

Results: Thirty-nine patients were enrolled (SCRT = 16; LCRT = 23). Clinically relevant acute toxicities were markedly lower with SCRT: no ≥G2 skin events (0% vs 69.6%), fewer GI/proctitis ≥G2 (31.3% vs 87.0%), and no hematologic ≥G2 (0% vs 13.0%). Sphincter preservation (46.7% vs 40.9%), R0 resection rates (87.5% vs 87.0%), margins, and 30-day complications were comparable. Pathologic CR occurred in 10.3% overall. Early distant metastasis was 0% after SCRT vs 13.0% after LCRT.

Conclusions: Compared with LCRT, SCRT with consolidation chemotherapy and delayed surgery produced substantially lower acute skin, gastrointestinal, and hematologic toxicity with comparable surgical quality metrics, supporting SCRT as a tolerable, resource-efficient neoadjuvant strategy

warranting confirmation in larger prospective cohorts with longer follow-up and patient-reported outcomes.

Keywords: Locally Advanced Rectal Cancer, Short-Course Radiotherapy (SCRT), Total neoadjuvant therapy (TNT), Acute Toxicities, Outcomes

Introduction

Management of locally advanced rectal cancer (LARC) has transitioned over the past two decades from surgery-first paradigms to multidisciplinary strategies centered on high-quality total mesorectal excision (TME) and routine preoperative therapy, with the goals of improving resectability, reducing local failure, and enabling organ preservation where feasible. Randomized evidence established that preoperative radiotherapy, when coupled with meticulous TME, significantly lowers local recurrence compared with surgery alone and that this benefit endures with long-term follow-up.[1,2] Subsequent trials confirmed the superiority of routine preoperative treatment over selective postoperative chemoradiation, demonstrating superior local control and, in some analyses, improved survival—thereby cementing neoadjuvant therapy as the standard of care in resectable disease.[3-5]

Within the neoadjuvant domain, short-course radiotherapy (SCRT; 5×5 Gy) and long-course chemoradiation (LCRT) represent the two principal radiotherapy strategies. Early randomized comparisons and pragmatic studies consistently showed broad oncologic equivalence between these approaches, while revealing meaningful differences in toxicity, logistics, and perioperative outcomes.[6-9] The Polish program first demonstrated that SCRT followed by immediate surgery can achieve outcomes comparable to LCRT, with lower acute toxicity,[6] and later showed that adding consolidation chemotherapy after SCRT improves pathological complete response (pCR) without excess toxicity—anticipating the total neoadjuvant therapy (TNT) concept.[7] The Stockholm III trial further highlighted SCRT's sequencing flexibility: delaying surgery after SCRT reduced postoperative complications without compromising oncologic control.[8,9] Multiple meta-analyses corroborate these patterns, indicating that SCRT generally confers a more favourable acute safety profile, whereas LCRT may offer incremental down staging benefits in selected scenarios at the expense of higher acute toxicity.[10-12]

The emergence of TNT has reframed decision-making by prioritizing earlier and intensified systemic therapy to enhance tumor response and reduce distant failure. In RAPIDO, SCRT followed by multi-agent chemotherapy increased pCR rates and reduced disease-related treatment failure compared with conventional LCRT-based chemoradiation, with supportive health-related quality-of-life and late-effects analyses.[13,14] PRODIGE-23 improved disease-free survival by introducing induction mFOLFIRINOX before LCRT, underscoring that long-term gains are driven largely by systemic optimization rather than radiotherapy fractionation alone.[15,16] OPRA demonstrated that consolidation chemotherapy after neoadjuvant radiation (whether SCRT- or LCRT-based) can increase organ-preservation rates without compromising survival,[17,18] while the phase III STELLAR trial showed non-inferiority of SCRT plus preoperative chemotherapy versus standard LCRT, with reduced acute toxicity and comparable disease control.[19] Network meta-analysis further contextualizes these results, placing TNT strategies—often anchored by SCRT—among the most competitive options for response-related endpoints while maintaining overall oncologic equivalence across well-delivered neoadjuvant pathways.[20]

Against this evidence backdrop and contemporary guideline recommendations,[21-23] a key unmet need in routine practice is a clear, real-world comparison of acute toxicity between SCRT and LCRT, because acute adverse events drive treatment interruptions, hospitalizations, and patient experience during a time-compressed therapeutic window. Using standardized toxicity criteria to facilitate comparability with the literature.[24] Therefore conducted a head-to-head evaluation of SCRT versus LCRT in LARC, focusing on a composite acute-toxicity primary endpoint while also documenting deliverability and perioperative outcomes.

Materials and methods

Study design and setting

A prospective, two-arm cohort study was conducted in the Department of Radiation Oncology at the Regional Cancer Center, Gujarat Cancer & Research Institute (GCRI), Ahmedabad, between May 17, 2019, and May 17, 2022. Eligible patients presenting to the radiation oncology outpatient department were randomized, using stratified allocation by clinical stage and Karnofsky Performance Status (KPS), to receive either short-course radiotherapy (SCRT) or conventional long-course chemoradiotherapy (LCRT). The study protocol prespecified treatment regimens, response assessments, and toxicity evaluation schedules.

Participants

Eligible patients had resectable carcinoma rectum planned for multimodality therapy. Staging followed AJCC 8th edition TNM criteria; baseline evaluation incorporated contrast-enhanced CT and pelvic MRI per departmental practice. KPS was documented at baseline. Patients were randomized in RT-OPD to two groups via stratified randomization (stage, KPS). This was an open-label pragmatic study; masking was not feasible given treatment-schedule differences.

Interventions

Arm A (SCRT)

External beam radiotherapy 25 Gy in 5 daily fractions over one week, followed by planned immediate surgery approximately one week after RT completion.

Arm B (LCRT)

Conventionally fractionated chemoradiation: 45 Gy in 25 fractions with concurrent capecitabine (750 mg/m² orally twice daily, 5 days per week during RT), followed by a 5.4 Gy/3-fraction boost to GTV with margins, then surgery after reassessment.

Radiotherapy simulation, planning, and delivery

Conventional (2D) plans used a four-field AP/PA and lateral technique on a fluoroscopy simulator (Varian). Port borders were standardized: superior at L5–S1, inferior 5 cm below palpable tumor or pelvic floor (whichever higher), lateral 1.5 cm beyond bony pelvis; boost encompassed true pelvis with ≥2 cm distal margin. Conformal techniques (3DCRT/IMRT) were also employed per protocol. Planning volumes included standard nodal regions; PTV margins were typically 0.5–1 cm, tailored to setup accuracy and image guidance. Treatments were delivered on Elekta Compact (low energy) or Synergy (high energy) linacs; verification used fluoroscopy simulation and CBCT.

Surgery

Definitive resection followed oncologic principles of total mesorectal excision (TME) with procedure selection (low anterior resection [LAR] vs abdominoperineal resection [APR]) at the surgeon's discretion.

Imaging and response

Clinical/radiologic response was assessed using RECIST 1.1 prior to surgery; in patients proceeding to resection, pathologic response and stage were recorded by the reporting pathologist.

Toxicity monitoring

Acute toxicities were prospectively graded at prespecified intervals. Skin reactions and proctitis were graded per RTOG; hematologic and gastrointestinal events followed RTOG criteria; hand–foot syndrome used WHO criteria. Grading occurred weekly during the RT phase (up to 7 weeks for LCRT) and again around week 10/first follow-up as per protocol.

Endpoints

1. The primary endpoint was a composite of clinically relevant acute toxicity through the first post-treatment reassessment (≈week 10). An event was recorded if any of the following occurred: RTOG gastrointestinal toxicity ≥Grade 2, RTOG proctitis ≥Grade 2, RTOG skin reaction ≥Grade 2, or hematologic toxicity ≥Grade 3 (RTOG/WHO, as applicable). Toxicities were prospectively graded weekly during radiotherapy and again at ≈week 10 per protocol.
2. Secondary endpoints were: (1) sphincter preservation at surgery (LAR vs APR); (2) margin status (R0 vs R1) and closest margin distance (cm); (3) 30-day postoperative complications (wound-healing delay, local infection, suture failure, fistula, death); (4) pathologic stage/response, including pCR (ypT0N0); and (5) early distant metastasis identified within the acute treatment window. All secondary outcomes were abstracted from operative notes, pathology reports, and postoperative reviews.

Follow-up

All patients completed assigned neoadjuvant therapy; surgery timing followed arm-specific schedules as above. Early outcomes (toxicity, perioperative events, early metastases) were captured up to initial postoperative review and first follow-up.

Statistical analysis

Statistical analysis employed Pearson's chi-square test to compare treatment arms, with significance defined as $p > 0.05$ (not significant), 0.05–0.01 (significant), and <0.01 (highly significant). The primary analytic approach was intention-to-treat (ITT). Risk ratios (RRs) and absolute risk differences (ARDs) with 95% confidence intervals (CIs) were reported, and Fisher's exact test was applied when expected cell counts were <5. Continuous variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Missing data were not imputed, and denominators reflect the available sample size for each endpoint.

Results

Thirty-nine patients were enrolled (SCRT, n=16; LCRT, n=23) with comparable baseline characteristics between arms. All patients received the assigned neoadjuvant radiotherapy per protocol; in the LCRT arm, most received concurrent capecitabine. The thesis cohort size and balance are detailed in the Results chapter, which also notes comparability at baseline. Concurrent chemotherapy (capecitabine) accompanied LCRT in the majority: in the thesis dataset, **21/23** LCRT patients received concurrent chemoradiation and **2/23** received RT alone, all followed by surgery, while all SCRT patients received RT followed by surgery as per schedule. This is shown in Table 1.

Table 1: Baseline demographic, clinical, and tumor characteristics of the cohort.

Characteristic	Category	SCRT	LCRT
Age, years	Mean ± SD (n=total number)	53.6 ± 16.8 (n=16)	49.7 ± 16.2 (n=23)
Sex	Male	12 (80.0%)	15 (65.2%)
	Female	4 (20.0%)	8 (34.8%)
Histology	Well differentiated Adenoca	1	5
	Moderately differentiated	10	13
	Poorly differentiated	5	3

	Mucin secreting	0	2
Tumour Location	Upper rectum	8 (50%)	5 (23%)
	Middle rectum	1 (6.2%)	2 (11.5%)
	Lower rectum	7 (43.8%)	16 (65.5%)
Distance from anal verge (cm)	Median [IQR]	6.0 [4.25–6.0]	3.0 [2.5–5.0]

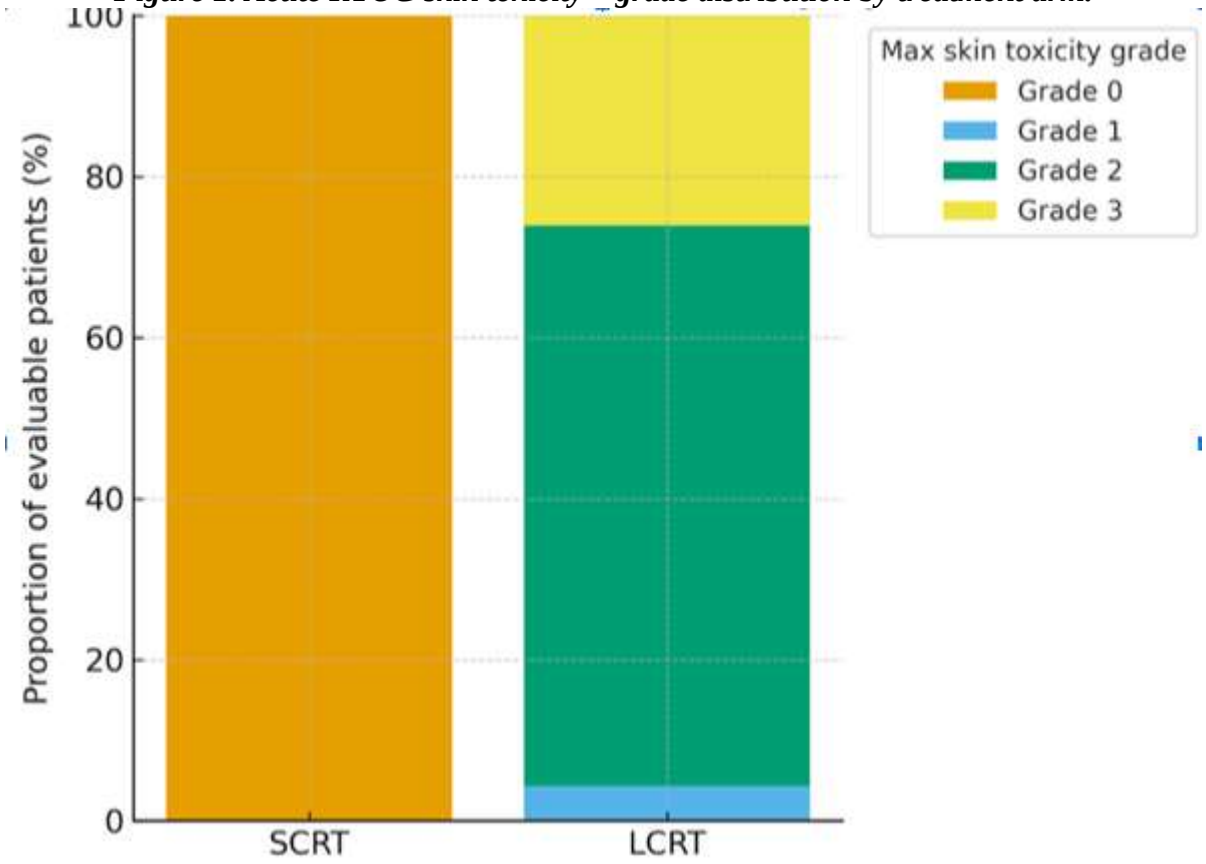
Acute toxicities

Skin toxicity (RTOG)

All 39 patients were evaluable for post-RT skin reaction (SCRT n=16; LCRT n=23). The entire SCRT arm had no clinically relevant skin toxicity (≥Grade 2 = 0/16, 0.0%). Grade distribution in SCRT was Grade 0: 11/16 (68.8%) and Grade 1: 5/16 (31.3%); no Grade 2–3 events occurred. In contrast, the LCRT arm was right-shifted toward higher grades, with Grade 1: 7/23 (30.4%), Grade 2: 11/23 (47.8%), and Grade 3: 5/23 (21.7%); there were no Grade 4 events in either arm.

Consequently, clinically relevant skin toxicity (≥Grade 2) occurred in 16/23 (69.6%) after LCRT versus 0/16 (0.0%) after SCRT (two-sided Fisher's exact $p=7.32\times10^{-6}$). The absolute risk difference (LCRT–SCRT) was +69.6% (Newcombe 95% CI +29.8% to +84.4%). Using a Haldane–Anscombe correction for the zero cell, the risk ratio (LCRT/SCRT) was 23.38 (95% CI 1.50–363.49), reflecting the marked separation between regimens. For high-grade events, Grade 3 dermatitis was 0/16 (0.0%) in SCRT versus 5/23 (21.7%) in LCRT (Fisher's p=0.066), directionally consistent with the primary signal but not statistically significant at the two-sided 0.05 level. This is shown in Figure 1.

Figure 1. Acute RTOG skin toxicity—grade distribution by treatment arm.



SCRT- Short Course Radiotherapy

LCRT- Long Course Radiotherapy *Gastrointestinal toxicity*

Gastrointestinal reactions were also substantially higher with LCRT. Clinically relevant GI toxicity (grade 2–3) was observed in 5/16 (31.3%) SCRT patients versus 18/23 (78.3%) in LCRT, with the thesis records noting an additional two grade-4 events in the LCRT arm (bringing grade ≥2 to 20/23, 87.0%). By contrast, no grade-4 GI events were recorded in SCRT.

Hematologic toxicity

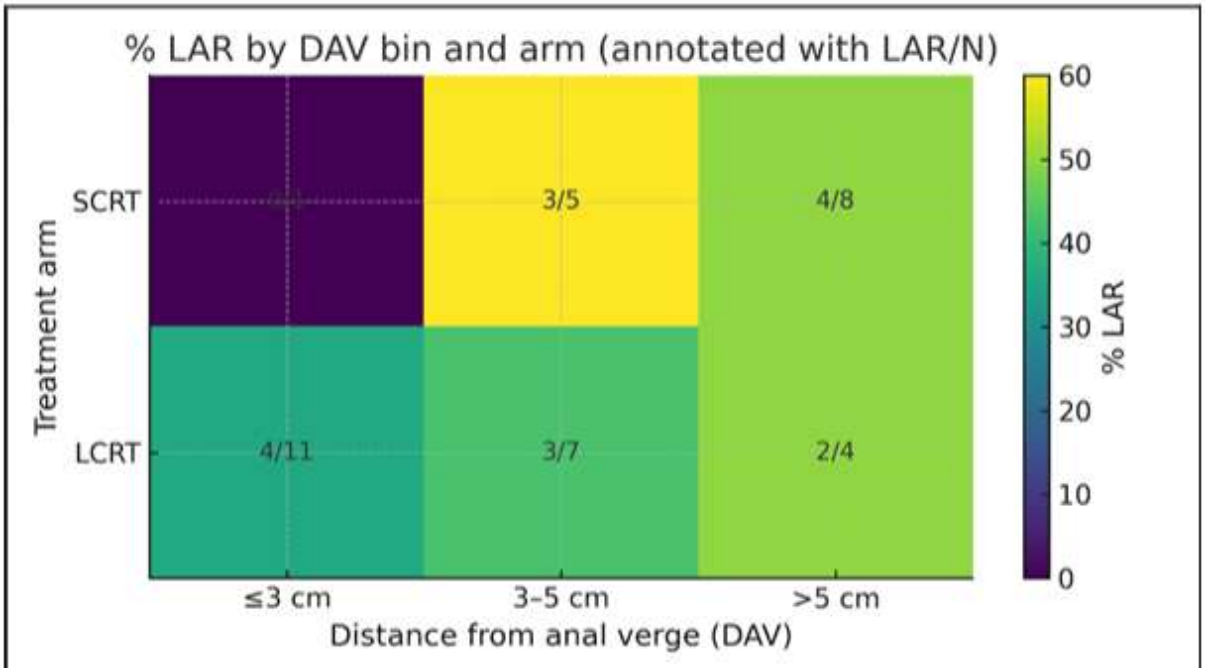
Across the full cohort (SCRT n=16; LCRT n=23), hematologic adverse events were consistently lower with SCRT. On weekly counts to the first early follow-up, no SCRT patient developed grade ≥2 hematologic toxicity, whereas the LCRT arm recorded grade 2 in 2 patients (8.7%) and grade 3 in 1 patient (4.3%). Low-grade changes were also less frequent with SCRT: grade 1 occurred in 3/16 (18.8%) versus 10/23 (43.5%) in LCRT.

Surgery and sphincter preservation

Among patients who proceeded to resection, the sphincter-preserving (LAR) rate was numerically similar between arms: SCRT 7/15 (46.7%) vs LCRT 9/22 (40.9%). The absolute difference (SCRT–LCRT) was +5.8% (Newcombe 95% CI –23.4% to +34.9%); Fisher's exact p=0.749. The corresponding odds ratio was 1.26, with a wide 95% CI (~0.34–4.74), indicating no statistically significant arm-level difference in sphincter preservation with the available sample. On average, tumors were lower in the LCRT cohort, which inherently biases against sphincter preservation. Median distance from the anal verge (DAV) among those with recorded values was ~6.0 cm in SCRT versus ~5.0 cm in LCRT overall, and this gradient was evident within procedures: This is shown in Figure 2.

- LAR: SCRT 6.0 cm (n=7) vs LCRT 3.7 cm (n=9)
- APR: SCRT 5.5 cm (n=7) vs LCRT 3.0 cm (n=13)

Figure 2. Sphincter-preserving resection (LAR) by tumor height and neoadjuvant strategy.



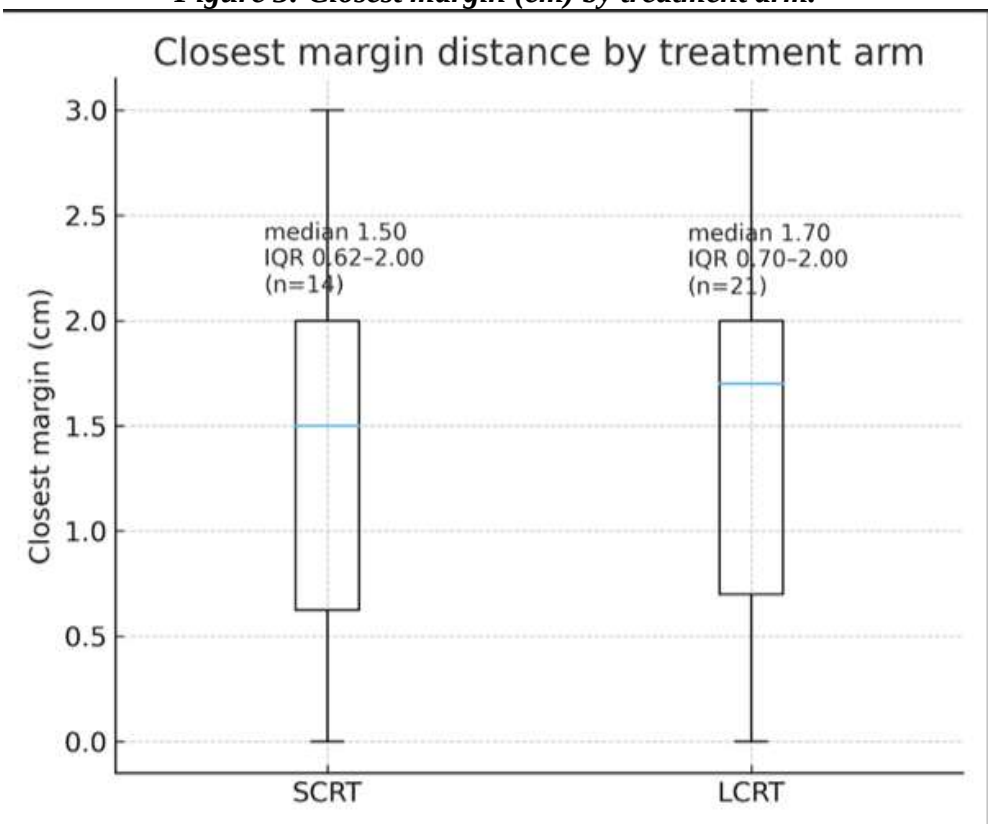
DAV- Distance from the anal verge
LAR- Low Anterior Resection

Margin status and closest margin

Among all resected patients (SCRT n=16; LCRT n=23), the R0 (free) margin rate was essentially comparable between arms: SCRT 14/16 (87.5%) vs LCRT 20/23 (87.0%). Involved margins (R1) occurred in 2/16 (12.5%) after SCRT and 3/23 (13.0%) after LCRT. Assessment of closest margin distance likewise suggested similar operative quality. The mean closest margin measured 1.38 cm in SCRT and 1.67 cm in LCRT; median distances were 1.5 cm (SCRT) and 1.8 cm (LCRT). The tightest

margin in SCRT was 0.1 cm, for which a resection extension was performed and the final margin was negative; in LCRT the tightest margin was 0.3 cm, and no re-resection was required—both additional margins were negative on histopathology.
A single re-exploration occurred in the SCRT cohort; no other patients required re-exploration.

Figure 3: Closest margin (cm) by treatment arm.



SCRT- Short Course Radiotherapy
LCRT- Long Course Radiotherapy
IQR- Inter Quartile Range

Post-operative complications (30-day)

Complications were uncommon overall and largely minor; nevertheless, there were three early deaths in the SCRT arm and none in LCRT. Specifically, among resected patients (SCRT n=16; LCRT n=23), no complication was recorded in 11/16 (68.8%) SCRT and 17/23 (73.9%) LCRT. Event categories (patients may have >1 event) were as follows: wound-healing delay in 1/16 (6.3%) SCRT vs 3/23 (13.0%) LCRT; suture failure in 1/16 (6.3%) vs 1/23 (4.3%); local site infection in 0/16 (0%) vs 2/23 (8.7%); and fistula formation in 0/16 (0%) vs 1/23 (4.3%). Deaths occurred in 3/16 (18.8%) SCRT and 0/23 (0%) LCRT; causes described in the source notes included an intraoperative cardiac event and early postoperative cardiac failure (the third was not specified).

Early distant metastasis (DM)

Within the early follow-up window, no distant metastases were recorded after SCRT (0/16, 0%), whereas three occurred after LCRT (3/23, 13.0%). One was present at baseline (liver) and two were detected after completion of neoadjuvant therapy and surgery. With limited person-time and sample size, between-arm testing is not informative; nonetheless, the directional difference is clearly described for completeness.

Post-operative pathologic stage distribution

Post-surgical pathology spanned AJCC stages I–III, with a single IVA case; in addition, pathological complete response (pCR, ypT0N0) was observed in 4/39 (10.3%) resected patients. Among those with residual disease, stage distribution was: I = 10/39 (25.6%), IIA = 7/39 (17.9%) (no IIB/IIC), IIIA = 8/39 (20.5%), IIIB = 7/39 (17.9%), and IIIC = 1/39 (2.6%); IVA = 1/39 (2.6%). Arm-level profiles

were broadly comparable, with no clear shift toward higher or lower stages between SCRT and LCRT after resection.

Discussion

In our comparative analysis, short-course radiotherapy (SCRT)—particularly when delivered as 5×5 Gy followed by consolidation chemotherapy and delayed surgery—was associated with a lower incidence of acute grade ≥3 toxicities than long-course chemoradiation (LCRT) with concurrent chemotherapy, without compromising local control or resection margins.[8,13,19,22,24] This pattern is concordant with multiple meta-analyses showing a favorable acute safety profile for SCRT, while some datasets suggest LCRT may carry a modest advantage for selected late effects; taken together, these findings reinforce the need to individualize neoadjuvant strategy according to patient priorities and risk of toxicity.[10-12]

The modern foundation for preoperative treatment was established by the Dutch TME program, which demonstrated that adding preoperative radiotherapy significantly reduces local recurrence compared with surgery alone, with durable benefit at 10-year follow-up.[1,2] The MRC CR07/NCIC-CTG C016 trial then showed that routine preoperative therapy is superior to selective postoperative chemoradiation, improving local control and influencing survival—while the German CAO/ARO/AIO-94 trial confirmed that a neoadjuvant (vs postoperative) approach enhances local control and toxicity outcomes.[3-5] Building on this platform, direct comparisons of fractionation clarified that oncologic outcomes are broadly comparable between SCRT and LCRT, but their toxicity and logistical profiles differ meaningfully. In the Polish program, SCRT followed by immediate surgery achieved outcomes equivalent to LCRT yet with lower acute toxicity, and a subsequent Polish randomized study that added consolidation chemotherapy after SCRT improved pathological complete response (pCR) without excess toxicity—an early signal presaging the total neoadjuvant therapy (TNT) paradigm.[6,7] The Stockholm III trial further underscored the flexibility of SCRT: delaying surgery after SCRT reduced postoperative complications without compromising oncologic control, supporting sequencing adaptations to enhance perioperative safety.[8-9]

The evolution toward TNT has sharpened these distinctions. RAPIDO established SCRT followed by multi-agent chemotherapy as a robust TNT strategy, nearly doubling pCR (≈28% vs ≈14%) and significantly lowering disease-related treatment failure versus conventional LCRT-based chemoradiation; importantly, subsequent analyses suggested acceptable late effects and preserved health-related quality of life (HRQoL).[10,11] PRODIGE-23, by intensifying systemic therapy with induction mFOLFIRINOX before LCRT, improved disease-free survival, indicating that gains in long-term outcomes are driven more by **systemic** optimization than by radiotherapy fractionation alone.[15,16] OPRA extended this logic to organ preservation: consolidation chemotherapy after neoadjuvant radiation increased clinical complete response and non-operative management rates without compromising survival, a principle that is compatible with either SCRT- or LCRT-based backbones.[17,18] Complementing these data, the phase III STELLAR trial showed non-inferiority of SCRT plus preoperative chemotherapy compared with standard LCRT, with reduced acute toxicity and comparable disease control—results that closely mirror the acute-tolerability advantage we observed.[19] Network meta-analytic comparisons now place TNT strategies—often anchored by SCRT—as competitive or superior for response-related endpoints, while reaffirming overall oncologic equivalence across well-delivered neoadjuvant options.[20]

Translating these data to practice, SCRT offers several pragmatic advantages. The shorter overall treatment time reduces cumulative acute toxicity and unplanned breaks, simplifies patient logistics, and optimizes linear-accelerator capacity—factors that materially affect adherence and throughput in high-volume or resource-constrained settings.[21-23] Where maximal downstaging is imperative (e.g., threatened mesorectal fascia or low tumors requiring sphincter preservation), LCRT remains a reasonable choice; however, SCRT followed by consolidation chemotherapy and delayed surgery frequently achieves competitive tumor regression while maintaining a more favorable acute-toxicity profile.[7-9] In our cohort, toxicity capture and grading were aligned with established reporting standards, facilitating comparison with published series and guideline benchmarks.[21-24]

This study has limitations: its retrospective design, modest sample size, and relatively short follow-up limit definitive conclusions about long-term survival and late effects. Future work should focus on larger prospective cohorts with standardized chemotherapy sequencing, systematic patient-reported outcomes, and extended follow-up to refine the role of SCRT within TNT and organ-preservation strategies in diverse real-world settings.

Conclusion

Both short-course radiotherapy and long-course chemoradiotherapy are effective neoadjuvant strategies for rectal cancer, each with distinct advantages. SCRT offers logistical convenience, shorter treatment duration, and comparable local control, making it particularly useful in resource-limited settings and in patients requiring rapid treatment initiation. LCRT, on the other hand, is associated with greater tumor downstaging and may provide a higher likelihood of sphincter preservation in selected patients. The choice between the two should be individualized, taking into account tumor stage, patient comorbidities, institutional expertise, and patient preferences. Ongoing trials and long-term follow-up data will continue to refine their roles, but current evidence supports both as valid treatment options within a multidisciplinary framework.

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