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Preoperative Short-Course Radiotherapy with Delayed Surgery Versus Long-Course Chemoradiotherapy for Locally Advanced Rectal Cancer

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ABSTRACT

Background: In multiple studies, preoperative long-course radiotherapy (PLRT) in conjunction with concurrent chemotherapy (PLCRT) and preoperative short-course radiotherapy (PSRT) with immediate surgery have demonstrated comparable outcomes regarding late morbidity, local control, and prolonged survival. However, long-course RT demonstrated a more favorable pathological complete response (PCR). The acute radiation toxicities associated with the short-course program are considerably lower than those observed in standard CRT. Significant benefits are associated with postponing surgery after neoadjuvant therapy for rectal cancer. As a result, a strategy of short-course RT and then consolidation chemotherapy prior to surgical resection is developed to achieve these benefits.

Objective: This study aimed to evaluate the treatment outcome, safety, and feasibility of preoperative short-course hypo fractionated RT (SCRT) followed by chemotherapy versus standard conventional long-course concurrent chemoradiotherapy (LCRT) for locally advanced rectal cancer (LARC) patients.

Patients and methods: This phase II prospective trial included 59 patients through the period from May 2020 to February 2021 in Sohag Cancer Center and Sohag University Hospital with a median follow-up of 31 months (range 4:37). Thirty cases were assigned to the experimental group (SCRT) and twenty-nine were assigned to the standard group (LCRT). The study was performed on locally advanced rectal cancer (LARC) cases and were randomized to neoadjuvant short-course RT followed by chemotherapy or preoperative conventional long-course CRT. Pathological response and treatment-related toxicity constituted the main endpoints. EFS, LFFS, DRFS, and OS were the secondary endpoints. **Results:** No significant variations were reported between the SCRT and LCRT groups as regards death rate and locoregional failure rate, or distant recurrence. In subgroup analysis for cases who were subjected to resection, no significant variations were reported between the SCRT and LCRT groups regarding postoperative (pathological) stages, pathological complete response rates, and grades of tumors. No significant variation was reported between the two groups as regards most of treatment-related toxicities, but the SCRT group had significantly lower radiation therapy-induced toxicities than the LCRT group.

Conclusion: Patients diagnosed with LARC may benefit from SCRT followed by chemotherapy as a substitute for conventional CRT. SCRT with delayed surgery showed comparable efficacy to conventional LCRT.

Keywords: Rectal cancer, Neoadjuvant radiotherapy, Long course, Short course.

INTRODUCTION

With an estimated 6.1% of all cancer cases, colorectal carcinoma is the third most prevalent malignancy worldwide in males and females. Additionally, it ranks as the second most frequent reason for cancer-related death (9.2%). In Egypt, colorectal cancer constitutes 4.2% and comes at 7th rank in both sexes (9th in men and 8th in women). The median age is 50 years [(1, 2)].

Neoadjuvant radiation treatment decreases local recurrence rates, preserves sphincter, and reduces radiation-induced toxicities in stage II and III rectal cancer cases with no variation within the 5-year overall survival (OS) [(3)]. Two preoperative radiotherapy (RT) methods are generally used. Firstly, standard long-course RT (LCRT) includes 45-50.4 Gy in 25-28 sessions with concurrent chemotherapy followed by surgical resection after 4-8 weeks. Secondly, short-course RT (SCRT) that consists of 25 Gy in 5 fractions then immediate surgery within one week or delayed surgery after more than 8 weeks [(4)].

Long course Chemotherapy did not increase OS, late toxicity, or local control compared to SCRT alone with immediate surgery. Cases subjected to long course were likely to have lower pathologic stages, lower rates of radial margin involvement, and higher pathological complete response rates [(5)]. These results of multiple RCTs compared preoperative standard CRT course then surgical resection versus SCRT then consolidation chemotherapy before surgery.

PATIENTS AND METHODS

This randomized phase II prospective comparative study was performed in Sohag University Hospital and Sohag Cancer Center. Pathological response and treatment-related toxicity constituted the main endpoints. **Secondary endpoints** were event-free survival (EFS), which is the time between the date of randomization to the initial development of locoregional failure (local recurrence, local progression, or irresectability within 6 months of preoperative treatment) or distant recurrence. Locoregional failure-free survival (LFFS) is the time between the dates of randomization to the first occurrence of locoregional failure. Distant recurrence/relapse-free survival (DRFS) that is defined as the time between the dates of randomization to the first occurrence of distant metastasis. OS is the interval of time between the date of randomization to the last follow-up or death date. Disease-free survival (DFS is the interval of time

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between the date of surgery to the last follow-up date or first occurrence of local recurrence or distant metastasis. Locoregional recurrence-free survival (LRFS), which is the interval of time from surgery date to the initial occurrence of local recurrence date.

Eligibility criteria: Age between 20 and 70 years. Pathological confirmation of rectal adenocarcinoma. Locally advanced rectal carcinoma (≥T3 or N+). Patient evaluated by surgeon and found to be a potential surgical candidate. Absence of other malignancy or distant metastases. Not a single comorbid condition that might compromise the patient's survival.

Randomization: The patients were randomized using stratified randomization methods to reduce heterogeneity between treatment groups. Patients were stratified according to their disease site (distance from the anal verge), grade, and gender.

Ethical approval: The study received approval from The Academic and Ethical Committee of Sohag University. Each patient provided written informed consent to receive the therapy. This research was conducted in adherence to the World Medical Association's Code of Ethics (Declaration of Helsinki) including human subjects.

Work up: A thorough examination and complete history were proposed for all participants. MRI pelvis for accurate tumor, nodal staging, and magnetic resonance fingerprinting (MRF) evaluation. Also, digital rectal examination, colonoscopy for biopsy and measuring distance from the anal verge, CT chest, CT abdomen and pelvis for distant metastasis, tumor markers CA 19.9 and CEA and baseline blood tests. After delivering of neoadjuvant treatment, patients were re-evaluated by MRI pelvis to assess response to neoadjuvant therapy and CT chest, abdomen, and pelvis for distant metastasis.

Treatment procedure: Patients randomized to preoperative SCRT followed by chemotherapy and long-course concurrent chemoradiotherapy.

Arm (A): Short course arm:

- Preoperative doses of Radiation: 25 Gy in 5 fractions given over 1 week.
- **Drug:** FOLFOX4 regimen: Leucovorin 200 mg/m^2 i.v. and 5-FU 400 mg/m^2 i.v. bolus followed by 5-FU 600 mg/m^2 i.v. 22 h-infusion day 1 + 2, oxaliplatin 85 mg/m^2 day 1. Repeat every 2 weeks for about 16 weeks or CAPOX regimen: oxaliplatin 130 mg/m^2, once daily, on day 1 and capecitabine 1,000 mg/m^2, twice a day, from day 1 to day 14 for about 15 weeks) at 14 -18 days after completion of RT.
- **Surgery:** Radical rectal cancer resection after 3-5 weeks after completing chemotherapy.

Arm (B): Long course arm:

- Preoperative doses of radiation: 50.4 Gy in 28 fractions to the pelvis, five fractions per week, one fraction per day concurrent with chemotherapy capecitabine (825 mg/m^2, twice a day) daily with RT.
- Surgery: Radical rectal cancer resection 4-6 weeks after completion of RT.
- Drugs: adjuvant chemotherapy FOLFOX regimen or CAPOX regimen for 6 months after recovery from surgery.

Radiotherapy technique

- Eligible patients were treated and contoured according to the radiation therapy oncology group (RTOG) contouring guidelines. Patients received 3-D conformal RT. The primary tumor, nearby lymph nodes, and at-risk pelvic regions were all included in the clinical target volume (CTV). The internal iliac nodes, obturator nodes, mesorectum, and presacral area were all covered by the CTV. Furthermore, when rectal tumor staged T4b, external lilac nodes should be included. Two to three centimeters separated the inferior border from the tumor's bottom pole. To achieve the planning target volume, the CTV expanded by 0.5–1.0 cm.
- Treatment plans assessed using the ICRU83 recommendation as the following:
  1. According to the RTOG recommendation, using the cumulative DVH to ensure that the maximum dose is limited to 107%, the minimum dose to the target is 95%, also, the dosage administered to the organ at risk will be minimized.
  2. Differential dose-volume histogram (DVH) and standard deviations of the dosage will be utilized to evaluate dose homogeneity.
  3. Dose gradient measurement and conformity index will be calculated.
- Setup error, random, and systemic errors were checked using electronic portal imaging device (EPID) daily for each patient in the SCRT group and weekly in the LCRT group.
- Assessment of radiation therapy acute toxicities according to the RTOG recommendations: Cutaneous toxicity, urinary tract toxicity, and gastrointestinal toxicity were categorized.

Pathology assessment: Pathological staging was determined by analyzing the surgical specimen. Tumor samples were obtained to determine the tumor's histology type, grade, lymphovascular invasion, direct tumor spread, tumor deposits, and perineural invasion. Evaluation of the impact of neoadjuvant therapy: **Ryan *et al.*** [6] modified system was utilized to grade tumor response following the AJCC Cancer Staging Manual (8th edition) and the CAP guidelines:

0 -Complete response: No viable cancer cells remaining.

1 - Moderate response: Singular cancer cells or small clusters persist.

2 - Minimal response: Prominent fibrosis accompanies the residual malignancy.

3 - Poor response: Extensive residual cancer; minimal or no tumor kill.

Follow up: During the initial two years, follow-up studies were planned every three months. Evaluation by clinical examination, laboratory tests, tumor markers level, chest and abdomen imaging, and pelvic MRI. Following up with all cases for a minimum of two years after surgery,
the final follow-up date was 30/8/2023.

Statistical analysis: STATA version 17.0 (Stata Statistical Software: Release 17.0 College Station, TX: Stata Corp LP.) was used for data analysis. Qualitative variables were displayed as numbers and percentages and compared using either the Chi-square test or the Fisher exact test. Quantitative variables were displayed as mean, standard deviation, median, and range. Due to the non-normal distribution of the data, the Mann-Whitney test was utilized to compare the two groups. Various survival categories were evaluated utilizing the Kaplan–Meier survival method in conjunction with the log-rank test. Utilizing Excel or the STATA programs, graphs were generated. The two-tailed p-value was deemed significant if it was ≤ 0.05.

RESULTS

Patient and disease characteristics:

We enrolled and randomly assigned 59 patients between May 2020 and February 2021 from Sohag Cancer Center and Sohag University Hospital with a median follow-up of 31 months (range 4-37) Thirty patients were assigned to the experimental group "SCRT "and twenty-nine were assigned to the standard group "LCRT ". The mean age in the current study was 43.27 ± 14.21 with a median of 41 (23-69) years.

We included 28 (47.46%) males and 31 (52.54%) females. Characteristics of the cases were well balanced between the two arms as shown in table (1).

A significant variation was reported between the two arms as regards the involvement of mesorectal fascia as it was positive in 93.33% and 72.41% in the SCRT and LCRT groups respectively (p=0.03).

No significant variation was reported between the two arms in other disease characteristics, but we noticed a considered difference in CT3N2 percentage between the two arms, which accounted for 60.00% and 37.93% in the SCRT group and LCRT group respectively.

Table (1): Comparison between SCRT and LCRT groups as regards patient and disease characteristics

Variable		SCRT group- (N=30)	LCRT group (N=29	P value
Age/year	Mean ± SD Median (range)	45.13±14.31 42 (23:69)	41.34±14.10 40 (23:69)	0.27
Age/year	≤60 year >60 year	24 (80.00%) 6 (20.00%)	26 (89.66%) 3 (10.34%)	0.30
Gender	Male Female	14 (46.67%) 16 (53.33%)	14 (48.28%) 15 (51.72%)	0.90
T stage	T2 T3 T4a T4b	2 (6.67%) 27 (90.00%) 0 1 (3.33%)	4 (13.79%) 21 (72.41%) 4 (13.79%) 0	0.09
N stage	N0 N1 N2	1 (3.33%) 10 (33.33%) 19 (63.33%)	4 (13.79%) 7 (24.13%) 18 (62.06%)	0.59
Clinical stage	T2N1 T2N2 T3N0 T3N1 T3N2 T4N2	2 (6.67%) 0 1 (3.33%) 8 (26.67%) 18 (60.00%) 1 (3.33%)	1 (3.45%) 3 (10.34%) 4 (13.79%) 6 (20.69%) 11 (37.93%) 4 (13.79%)	0.15
Grade	1 2 3	2 (6.67%) 24 (80.00%) 4 (13.33%)	3 (10.34%) 23 (79.31%) 3 (10.34%)	0.84
Distance from the anal verge in cm	Mean ± SD Median (range)	4.83±2.64 4.5 (0:10)	5.93±3.62 5 (1:12)	0.41
Distance from the anal verge	≤5 cm >5 cm	21 (70.00%) 9 (30.00%)	17 (58.62%) 12 (41.38%)	0.36
Enlarged LN	Negative Positive	19 (63.33%) 11 (36.67%)	17 (58.62%) 12 (41.38%)	0.71
Mesorectal fascia	Negative Positive	2 (6.67%) 28 (93.33%)	8 (27.59%) 21 (72.41%)	0.03

Surgery and chemotherapy regimen:

Of the 59 patients, 20 did not undergo surgery due to different causes. Two (22.22%) cases in the SCRT arm and one (9.09%) case in the LCRT arm refused surgery.

One patient in each arm achieved a total clinical response and enrolled in the watch-and-wait protocol. Three (33.33%) cases in the SCRT group and 5 (45.45%) cases in the LCRT group were reported to be inoperable within 6 months of beginning neoadjuvant therapy by the treating surgeon. Unfortunately, one (11.11%) patient in the SCRT arm and 3 (27.27%) patients in the LCRT arm developed distant metastasis during preoperative treatment. Also, two (22.22%) cases in the SCRT arm and 1 (9.09%) case in the LCRT arm died during perioperative treatment due to high-grade toxicity.

Thus, surgery with curative purpose was performed on 18 (62.07%) of 29 patients in the LCRT group and 21 (70%) of 30 cases in the SCRT group within six months of the start of preoperative treatment.

As regards the type of chemotherapy regimen or type of surgical approach, no variations were reported between the two groups. As regards treatment-related toxicity, there were no significant variation was reported between the two groups as regards most of toxicities. SCRT group had significantly lower prevalence of diarrhea than LCRT group (p-value <0.0001), eleven cases in the control group and no cases in the study group developed grade 3 or 4 diarrhea. Also, SCRT group had significantly lower prevalence of cystitis than LCRT group (p-value <0.0001), only one case in the study group developed grade one cystitis. There was an absence of dermatitis in the study arm (p <0.0001) (Table 2).

Table (2): Comparison between SCRT and LCRT groups as regards side effects of treatment

Variable	SCRT group N=30	LCRT group N=29	P value
Cystitis			
No toxicity	29 (96.67%)	1 (3.45%)	<0.0001
Grade 1	1 (3.33%)	10 (34.48%)	
Grade 2	0	12 (41.38%)	
Grade 3	0	6 (20.69%)	
Diarrhea			
No	11 (36.67%)	0	
Grade 1	12 (40.00%)	4 (13.79%)	<0.0001
Grade 2	7 (23.33%)	14 (48.28%)	
Grade 3	0	8 (27.59%)	
Grade 4	0	3 (10.34%)	
Abdominal pain			
Grade 1	12 (40.00%)	12 (41.38%)	0.70
Grade 2	13 (43.33%)	10 (34.48%)	
Grade 3	5 (16.67%)	7 (24.14%)	
Dermatitis			
No	30 (100%)	6 (20.69%)	<0.0001
Grade 1	0	14 (48.28%)	
Grade 2	0	8 (27.59%)	
Grade 3	0	1(3.45%)	
Neuropathy			
No	2 (6.67%)	1 (3.45%)	
Grade 1	15 (50.00%)	10 (34.48%)	0.54
Grade 2	6 (20.00%)	9 (31.03%)	
Grade 3	7 (23.33%)	9 (31.03%)	
Hand foot syndrome			
No	28 (93.33%)	27 (93.10%)	0.57
Grade 1	1 (3.33%)	1 (3.45%)	
Grade 2	0	1 (3.45%)	
Grade 3	1 (3.33%)	0	
Fatigue			
Grade 1	16 (53.33%)	10 (34.48%)	0.25
Grade 2	10 (33.33%)	11 (37.93%)	
Grade 3	4 (13.33%)	8 (27.59%)	

Outcomes:

No significant variation was reported between the SCRT and LCRT groups as regards death rate, locoregional failure rate, or distant recurrence. The mortality rate in the studied population was 23.98%, nine patients died in the SCRT group and fourteen died in LCRT (p-value 0.15). Overall survival rates at 3 years were 70% in SCRT versus 51.7% in the LCRT group (p-value 0.15) as shown in figure (1). Locoregional failure which included cases with irresectability within 6 months of treatment, local recurrence after surgery, or local progression occurred in 10 patients (33.33%) in SCRT and 13 (44.83) patients in the LCRT group with no significant variation in locoregional failure-free survival at 3 -years (Figure 2).

Only eight cases in the study group and 12 cases in the control group developed distant metastasis (p-value 0.36). As regards the Site of distant recurrence, the lung was the most common site accounting for 35% of cases that developed distant recurrence (Table 3).

Table (3): Comparison between SCRT and LCRT groups as regards outcome

Variable		SCRT group (N=30)	LCRT group (N=29)	P value
Death	No	21 (70.00%)	15 (51.72%)	
	Yes	9 (30.00%)	14 (48.28%)	0.15
Locoregional failure	No	20 (66.67%)	16 (55.17%)	
	Yes	10 (33.33%)	13 (44.83%)	0.37
Distant recurrence	No	22 (73.33%)	17 (58.62%)	
	Yes	8 (29.63%)	12 (41.38%)	0.36

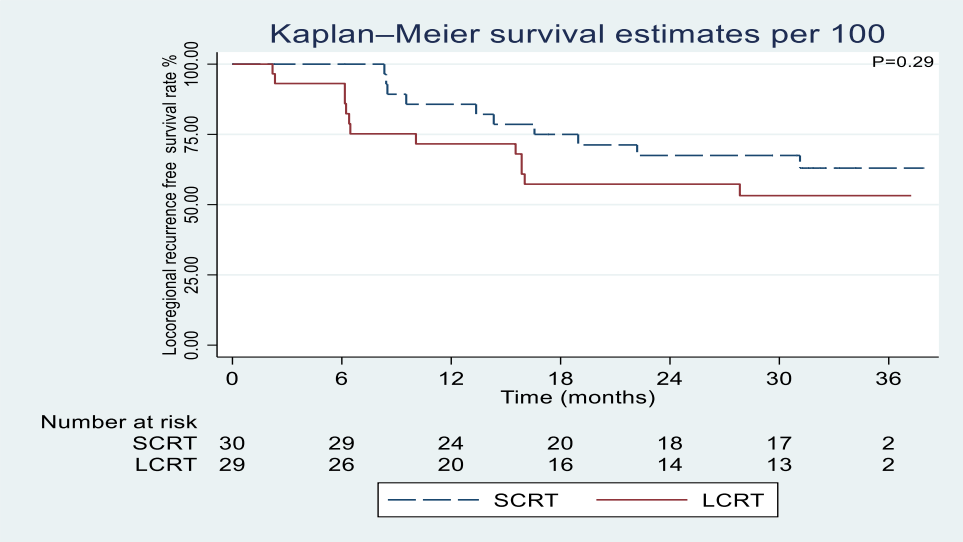

Figure 1: The overall survival rate in all patients by (groups).

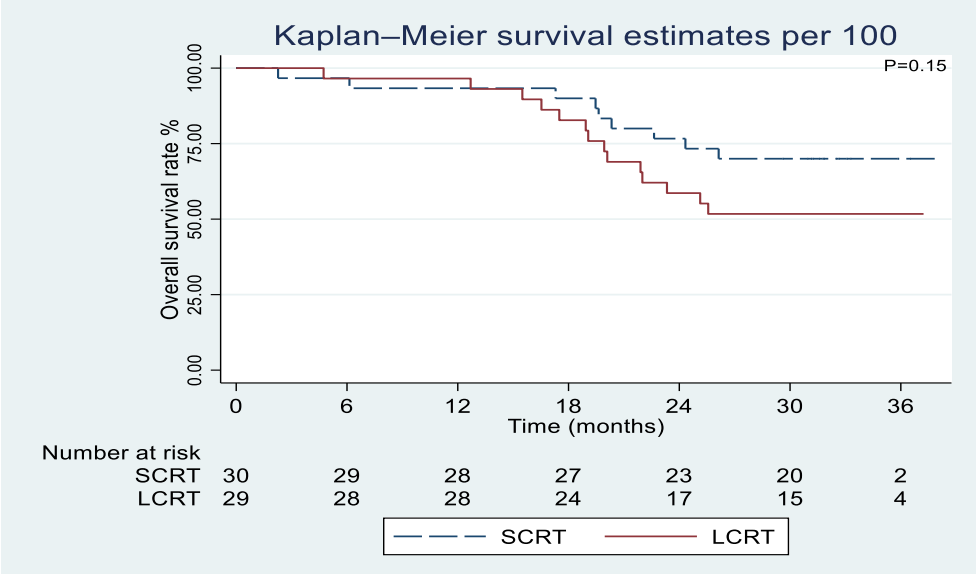

Figure (2): Locoregional failure- free survival rate in all patients by (groups)

Subgroup analysis: In subgroup analysis for cases who underwent resection, no significant variation was reported between the SCRT and LCRT groups as regards postoperative (pathological) stages and grades of tumors. Out of 39 cases who underwent radical resection, 10 (25.64%) patients achieved pathological complete response; seven patients (33.33%) in the SCRT group and three patients (16.67%) in LCRT (p-value 0.64). The tumor regression score for patients who failed to achieve PCR was reported. Nine patients (23.08%) scored 1, eleven (28.21%) patients scored 2, and nine (23.08%) patients scored 3. No significant variation was found between the SCRT and LCRT groups regarding local recurrence-free survival rates at 12 months, and 24 months. It was 85.45% and 83.33% at 2 years for SCRT and LCRT groups respectively (Figure 3).

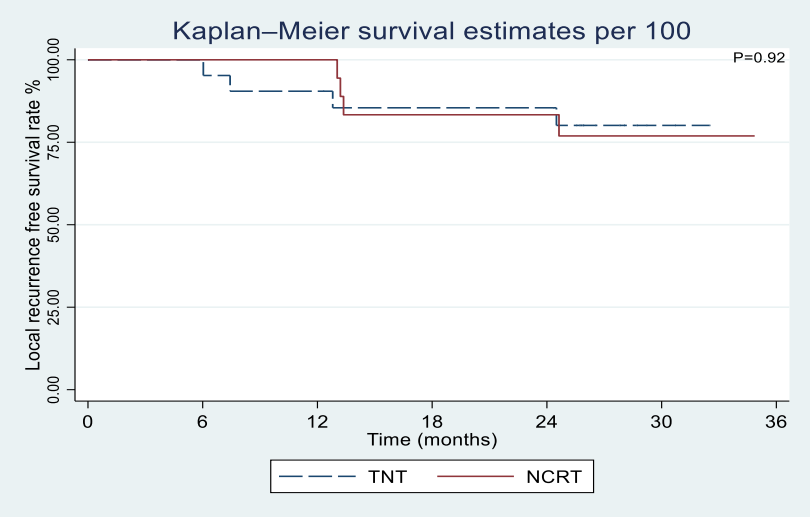

Figure (3): Local recurrence-free survival function over time in the studied population
------ SCRT _____ LCRT

DISCUSSION

Annually, 40,000 cases of intestinal cancer develop in the rectum, the most prevalent site of the disease, with the incidence rate being equal in both sexes. In recent decades, chemotherapy, RT, and surgery have been the most prevalent treatments for localized stage II and III rectal cancer. PLCRT and PSRT with immediate surgery are the two main neoadjuvant regimens established for rectal cancer disease [(3)].

Numerous investigations have demonstrated comparable local control, prolonged survival, and delayed morbidity for both approaches, but PCR was better in LCRT. The SCRT protocol provides an advantage over conventional CRT in that acute radiation toxicities are less common. Additionally, short-course RT is more practical and less costly, particularly in busy oncology institutions [(5)].

Significant benefits are associated with delaying surgery for rectal cancer after radiation: the potential for a full clinical response, additional time for patient optimization, and a decreased risk of postoperative complications. However, delaying the initiation of chemotherapy may raise the likelihood of disease progression and worse outcomes [(7)]. This concern evolves toward the practice of SCRT and then consolidation chemotherapy before operation.

The optimal regimen, PLCRT or PSRT with delayed surgery, has been the topic of continuous dispute. Recently, for the treatment of LARC, many trials have compared PSCRT with consolidation chemotherapy to conventional PLRT administered concurrently with chemotherapy. The current trial intended to evaluate the treatment outcome, safety, and the possibility of preoperative SCRT followed by scheduled chemotherapy versus standard chemoradiotherapy followed by TME and postoperative chemotherapy. We divided our patients into two groups: the SCRT group N=30 and the LCRT group (N=29).

An advantage of the current study is that our results showed no significant variation between the SCRT and LCRT groups in patient characteristics. This comes in line with almost all trials that investigated short-course RT strategies such as STELLAR and RAPIDO trials [(13, 14)].

Regarding the involvement of mesorectal fascia, a significant variation was reported between the two arms. Patients with positive mesorectal fascia accounted for 93.33% & 72.41% (P value .02) in the SCRT group and LCRT respectively. This comes in line with **Markovina *et al*** [(8)].

No significant variation was reported between SCRT and LCRT groups as regards other disease characteristics. Even though clinical stage T3N2 accounts for 60% and 37.93% in the SCRT group and LCRT group respectively, the variation was insignificant. This agrees with **Thakur *et al.*** [(5)] who enrolled a total of 28 cases with LARC. Thirteen patients were in the conventional RT group and 15 cases

were in the experimental group (SCRT group). They noticed that the two arms' patient characteristics (gender, age), and disease characteristics were similar. However, **Markovina *et al*. [8]** found a significant variation as regards the clinical stage between both groups. This difference may be due to different sample sizes.

We found no significant variation between SCRT and LCRT groups as regards most treatment-related toxicity, while a significant variation was found as regards cystitis, diarrhea, and dermatitis, which favored the SCRT strategy. Patients who received conventional protocol showed a considerably greater frequency of cystitis, which was reported in 97% of patients. Dermatitis was not observed in the SCRT arm, while 80% of LCRT arm patients developed it. No patient in the SCRT arm developed grade 3 or 4 diarrhea versus eleven patients in LCRT. Abdominal pain was the most common observed toxicity in both groups. Inconsistent with current findings, an Australian/New Zealand study randomized 326 cases to either SCRT or long-course CRT and discovered that cases in the traditional arm developed major side effects. In contrast, individuals in the experimental group experienced higher persistent stomas rate. (e.g., rates of radiation dermatitis, 5. 6% vs 0%; P =0. 003). But STELLAR study demonstrated more grades 3 and 4 acute toxicities during preoperative treatment that was greater in SCRT group versus CRT group (26. 5% vs. 12. 5%; P. 001) [9, 14].

Pathological analysis for cases who were subjected to surgery in the current study revealed no significant variation between the two groups regarding postoperative (pathological) stages and grades of tumors. Even though the pathological complete response was achieved in seven cases in the SCRT arm (33.33%) and only in three patients (16.67%) in the LCRT arm that was not statistically significant (P value 0.24). This may be the result of limited sample size, higher preoperative clinical stage T3N2 (60%) in SCRT group versus (37.93%) in LCRT. Moreover, there was statistically significant increased involvement of mesorectal fascia in SCRT (93.33%) than in LCRT (72.41%) group. This comes in line with the results of the STELLAR trial, which found that the rate of PCR was 16.6 % compared to 11.8 in SCRT/consolidation chemotherapy arm versus conventional CRT arm respectively with a p-value of 0.1. Also, the randomized Polish II study showed no significant variation in PCR between the SCRT/CCT group and the chemoradiation group (16% versus 12 % respectively) [10, 14].

In an effort to evaluate the existing information supporting preoperative SCRT then consolidation chemotherapy prior to surgical resection, a 2022 comprehensive review and meta-analysis identified around seventeen papers (RCTs, phase II trials, and retrospective studies). They demonstrated that employing this method increased sphincter preservation surgery, improved PCR rates, and the proportion of ypN0 status from initially involved regional nodes. The longer time between RT and surgery, during which systemic chemotherapy was administered, may have contributed to the increased PCR rate [12].

As regards the conventional neoadjuvant treatment, one critique of combining SCRT followed by immediate surgery in locally advanced rectal cancer was the limited time between procedures eliminates the potential for clinical tumor response. The experimental arm of the Stockholm III study exhibited a PCR rate increase of 11.8% if surgical resection was postponed for four to eight weeks following SCRT, as opposed to 2.1% in the SCRT with immediate surgery group [7]. Prior research has documented a higher pathological response to SCRT with delayed surgery, yet the rate of PCR did not surpass that of conventional CRT. In addition, the combined outcomes of this meta-analysis revealed that the PCR rate in group who received SCRT followed by delayed surgery without consolidation chemotherapy was much lower than that of traditional CRT. Thus, in the treatment of LARC, conventional CRT cannot be substituted with merely prolonging the time between SCRT and surgery in the absence of consolidation chemotherapy [12].

The improvement in PCR rates was also demonstrated in the RCT phase III RAPIDO trial, PCR rates were 28 % versus 14% in SCRT with consolidation chemotherapy versus conventional LCRT group respectively, P value <0.0001. Patients and tumor characteristics were well-balanced in this trial [13].

Current findings demonstrated that the SCRT and LCRT groups did not differ significantly from one another as regards outcomes (overall survival rates, locoregional failure rates, distant recurrence rates, and site of distant recurrence). Prior research revealed no significant variation between SCRT + CCT and conventional CRT in terms of LR rates or DM incidence based on a systematic review and meta-analysis performed in 2022 that aligns with the findings of the present trial [12].

In the randomized RAPIDO trial, which compared preoperative short-course (5 x 5 Gy) radiation therapy followed by chemotherapy to long-course (25–28 GY) chemoradiation therapy before surgery for cases with advanced rectal cancer, the DM rate at 3 years was 20.0% versus 26.8% in the two groups respectively (P value 0.005) [13]. Although the RAPIDO and PRODIGE-23 studies found that TNT reduced 3-year DM significantly, the Polish II and STELLAR trials did not. In these RCTs, the reported 3-year DM varied from 20% to 30% [10, 13, 14, 15]. In the current study, the rate of DR (DM) at 3 years was 28.66% versus 44.11% in the SCRT and LCRT groups respectively (p =0.27), with no significant variation between both groups, but higher rates of DR in the LCRT group. Rapido also reported no significant variation in locoregional failure rates at 3-years between the two arms which is also found in the current study [13].

STELLAR is phase III trial of 599 cases diagnosed stage II-III rectal cancer, comparing preoperative SCRT followed by chemotherapy to LCRT concomitant with chemotherapy. In the two groups TME was administered 6 to 8 weeks after preoperative treatment [14]. Local recurrence did not significantly differ between the two groups. The 3-year LR rates were 8.4% with TNT and 11.0% with CRT, which were lower than the Polish II trial but comparable to the RAPIDO and PRODIGE 23 trials [10, 13, 15].

In consistence with previous studies, sub-group analysis for cases subjected to radical resection in the current trial revealed no significant variation regarding local recurrence rate between the two arms. LRFS at 2 years was 85.45% and 83.33% in SCRT and LCRT groups respectively.

Current findings did not show that SCRT is better than LCRT as regards EFS, DFS, and OS. At 3-year OS was 70% versus 51.7 % in SCRT and LCRT groups respectively (P -value 0.15). In Polish II randomized trial, advanced rectal cancer cases were randomly allocated to receive either short-course radiotherapy followed by FOLFOX4 or only concurrent chemoradiotherapy before surgery. No variations in local efficacy or 3-year DFS between the arms was reported, but the short-course group had significantly higher 3-year OS (73% vs. 65%, P =. 046). However, this study's long-term findings indicated no significant variation in eight-year overall survival [10]. Consistent with the Polish II trial, STELLAR revealed that both CRT and TNT produced comparable 3-year DFS and better 3-year OS. OS in particular requires long-term follow-up to validate these conclusions, as the long-term results of Polish II demonstrated its disappearance [10].

In agreement with current findings, Stockholm III randomized trial, which compared SCRT to LCRT revealed no significant variation in DFS or OS between the randomized arms in long-term monitoring [7].

Current findings showed that 3 years, DFS was 75.89% and 50.00% in the SCRT and LCRT groups respectively.

Current findings support the strategy of SCRT followed by consolidation chemotherapy as it was able to achieve comparable locoregional control and survival benefit with high level of tolerability. The use of MRI for proper staging and evaluation of mesorectal fascia, as well as the reduction of the overall treatment duration without compromising results, are factors that support our study. Due to the limited sample size, no definitive conclusions for long-term outcomes can be derived.

CONCLUSIONS AND RECOMMENDATIONS

Our results suggest that in cases with LARC, neoadjuvant SCRT followed by chemotherapy may be a useful substitute for conventional CRT because it has the added advantage of having a lower toxicity profile and similar efficacy when compared to conventional LCRT concurrent with chemotherapy. In addition to a short treatment period, which is more convenient to patients and doctors, as well as less crowding over equipment in overcrowded centers. We recommend SCRT for use in developing countries and nations with limited access to radiation. Because of its shorter treatment time, lesser toxicity, and cheaper cost for supporting care. To confirm the results, additional study with longer follow-ups is necessary because the sample size was so small.

Limitations:

- The significant limitation was the limited sample size.
- The lack of outcomes reported by patients that would have enabled a difference to be made between anorectal and sexual functioning and quality of life.
- We did not include late toxicity of both techniques and surgical complications.

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Conflict of interest: The authors had nothing to declare.

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