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Research Article

Long-Course Chemoradiotherapy (LCRT) Shows Better Outcomes than Short-Course Chemoradiotherapy (SCRT) in Locally Advanced Rectal Cancer (LARC): Insights from Real World Data from A LMIC

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Abstract

Neoadjuvant treatment options like long course RT (LCRT)/Short course RT (SCRT)/ total neoadjuvant treatment (TNT) are the standard of care for locally advanced rectal cancer (LARC). We reviewed the departmental data of LARC for gaining an insight on treatment outcomes with LCRT and SCRT. We analysed data of database of LACR (2014-2020) and compared outcomes of LACR treated with SCRT or LCRT or no treatment. Out of 345 patients registered, complete information regarding treatment was available for 164 patients only. Two third of patients had lower one third tumor, the median tumor length was 6 cm, mesorectal fascia was involved in 42%, node positive were 83%. After LCRT (n=87)/SCRT(n=51), only 43% underwent surgery [low anterior resection:19%/ ultra-low anterior resection:1.5%,abdominoperineal resection:19.6%, and palliative surgery: 3%]. The median overall survival and disease-free survival in LCRT was 22 and 21 months and SCRT was 15 and 10 months (P <0.0001) respectively. On univariate analysis factors affecting OS and DFS were length of tumor, MRF involvement, pathological T status, pathological N status , and LCRT versus SCRT. On cox regression ypN positive (HR 2.9, p= 0.006) and type of RT (HR 273, p= 0.001) were retained as significant factors for OS and ypN positive (HR 2.9, p=0.01), and type of RT (HR 29, p=0.001were retained as significant factors affecting DFS. On Propensity score matching median OS and DFS with SCRT and LCRT was 20 months versus 40 months and 10 months versus 52 months respectively (p=0.01 and 0.002). Our data shows that the practice of LCRT results in better outcomes as compared to SCRT.

Keywords: Short-course radiotherapy; Long-course chemoradiotherapy; Total neoadjuvant treatment; Locally advanced carcinoma rectum; Low anterior resection syndrome.

Introduction

Colorectal cancer, is the third most common cancer worldwide. Although it is less common in India than in Western nations, it is nevertheless a serious problem.[1] The problem in low middle income countries (LMIC) is advanced stage at presentation. LARC comprises of T3–4 or node-positive disease and its treatment consists of a multidisciplinary approach that includes surgery, chemotherapy, and radiation therapy. The contemporary treatment of LARC is preoperative chemoradiotherapy (CTRT) followed by surgery. CTRT may be short course (SCRT), long course (LCRT) or total neoadjuvant treatment (TNT) followed by surgical options like LAR/ULAR or APR. TNT refers to administration of all cycles of systemic chemotherapy (CT) before surgery, whether it be prior to CTRT (Induction CT) or after CTRT (consolidation CT). This strategy aims to improve surgical outcomes, maximize tumor downstaging, and potentially increase the rates of pathological complete response (pCR) and organ preservation.[2,3] The pivotal trials (PRODIGE and RAPIDO) demonstrated the effectiveness of preoperative LCRT followed by consolidation CT (PRODIGE) or SCRT followed by consolidation CT (RAPIDO) in improved outcomes based on which ASCO guidelines recommended LCRT over SCRT in lower third LARC.[4] The higher pathological complete response rates (CR) rates and organ preservation rates with TNT is steering non-operative management options towards popularity in complete responders to CTRT. The efficacy of CTRT with its associated acute and chronic toxicities further complicates patient management, as evidenced by trials like PROSPECT, which emphasize the need for individualized approaches.[5] In a LMIC setup, disparities in healthcare access, socioeconomic factors, psychosocial factors like fear of stoma creation, body image issues, relief of symptoms from neoadjuvant treatment and cultural barriers and limited availability of multidisciplinary teams exacerbate poor outcomes, highlighting the need for equitable and personalized treatment strategies. The treatment of carcinoma rectum presents significant challenges, including variability in tumor biology, patient diversity, and systemic barriers. Tumor heterogeneity, such as the presence of aggressive subtypes like signet ring cell carcinoma and distinct molecular profiles (e.g., KRAS, BRAF mutations) and early onset rectal cancer impacts treatment planning and response to therapies.[6] While advancements like immunotherapy (e.g., PD-1 inhibitors for mismatch repair-deficient tumors) has changed the scenario for PDL1 positive tumours this strategy is applicable only to 10% patients.

The aim of this study is to evaluate real-world long-term outcomes of CTRT in a Regional cancer Centre in a LMIC set-up. We intend to compare the outcomes between LCRT versus SCRT in LACR and to assess the factors predicting outcomes. We also intend to identify the high risk features responsible for the various endpoints in a LMIC set-up. Following LAR, Low Anterior Resection Syndrome (LARS) is a common consequence seen in 41% patients and it has negative impact on patients' quality of life.[7] Hence the assessment of the incidence of low anterior resection syndrome (LARS) in survivors is also another endpoint. in ESCC.

Materials and Methods

We retrospectively analysed data of LACR (2014 - 2020) (Figure 1). Out of 345 patients, 164 patients were included in the study, distributed among three treatment groups LCRT (n=87), SCRT (n=51), and No Treatment (n=26) (Table 1) After obtaining histopathological proof of malignancy of the rectal mass and baseline disease status by MRI pelvis, patients were planned for either LCRT or SCRT according to physician preference and lack of clarity of superiority of LCRT over SCRT during that period. Due to waiting list of RT patients were initiated on induction CT (CAPOX). The dose of LCRT was 45GY/25fractions over 5 weeks along-with concurrent capecitabine at 1650mg/m2 (Monday to Friday) and that of SCRT was 25Gy/5 fraction in one week.

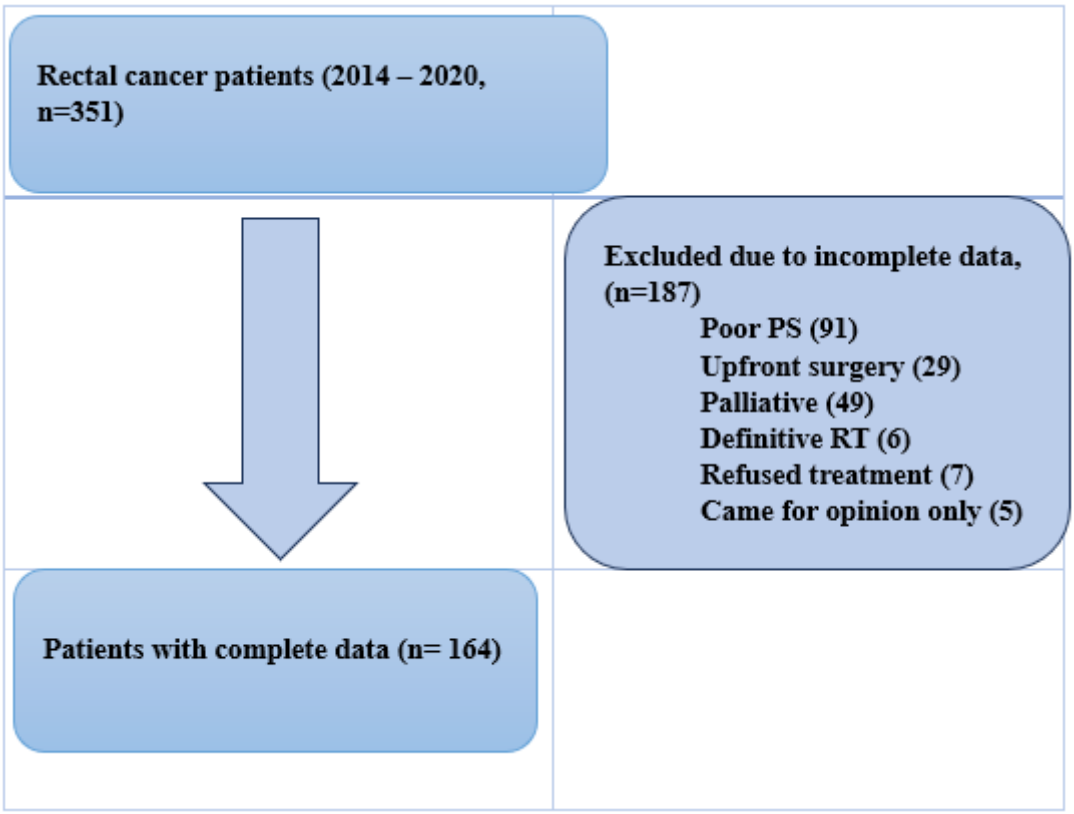

Figure 1: Consort diagram.

			LCRT	SCRT	Other Rx	p value
		n= 164 (%)	N (%)	N (%)	N (%)	
Age	Median age (range) [45 yr. (30 - 57)]					
Sex	Male	109 (66.5%)	52 (59.8%)	38 (74.6%)	19 (73.1%)	0.18
	Female	55 (33.5%)	35 (40.2%)	13 (25.4%)	7 (26.9%)	
Comorbidities	Present	16 (9.7%)	6 (6.8%)	9 (17.6%)	1 (3.8%)	0.08
	Absent	148 (90.3%)	81 (93.2%)	42 (82.4%)	25 (96.2%)	
Location	Upper 1/3rd	24 (14.6%)	12 (13.8%)	9 (17.6%)	3 (11.5%)	0.19
	Middle 1/3rd	34 (20.7%)	12 (13.8%)	14 (27.4%)	8 (30.8%)	
	Lower 1/3rd	106 (64.7%)	63 (72.4%)	28 (55%)	15 (57.7%)	
Length (cm)	≤ 6	92 (56%)	49 (56.3%)	31 (60.8%)	12 (46.2%)	0.2
	≥ 7	72 (44%)	38 (43.7%)	20 (39.2%)	14 (53.8%)	
MRF	Involved	69 (42%)	25 (28.7%)	25 (49%)	19 (73%)	0.006
	Not involved	95 (58%)	62 (71.3%)	26 (51%)	7 (27%)	
Clinical T	T3	125 (76.2%)	66 (75.8%)	43 (84.3%)	14 (53.8%)	0.36
	T4	34 (20.7%)	20 (22.9%)	8 (15.6%)	6 (23.1%)	

Clinical N	N0	28 (17.1%)	14 (16.1%)	8 (15.7%)	6 (23.2%)	0.08
	N1	77 (46.9%)	43 (49.4%)	24 (47.1%)	10 (38.4%)	
	N2	59 (36%)	30 (34.5%)	19 (37.2%)	10 (38.4%)	
Histopathology	Adenocarcinoma	129 (78.7%)	66 (75.9%)	41 (80.4%)	22 (84.6%)	0.18
	Mucinous	17 (10.4%)	10 (11.5%)	5 (9.8%)	2 (7.7%)	
	Signet ring	18 (10.9%)	11 (12.6%)	5 (9.8%)	2 (7.7%)	

Table 1: Demographic Characteristic.

After simulation (Somatom Sensation Open Multislice CT scanner with virtual simulation (M/s Siemens Medical System, Germany) target delineation was according to standard guidelines. [8] All patients received three-dimension conformal radiotherapy (3D-CRT) on a Linear Accelerator (VERSA HD, Elekta) or (CL2100CD, VARIAN) with 6MV photon beams. After 8 weeks of completion of RT an MRI pelvis was used to evaluate response to CTRT. This was to be followed by surgery which were LAR (low anterior resection)/ APR (abdominoperineal resection)/ ULAR (Ultra-low anterior resection)/ Exploration and debulking/ Colostomy only or Exenteration depending on position of tumour and extent of disease. The toxicity profile of the treatments was recorded and graded according to Common Terminology Criteria for Adverse Events (CTCAE v.3). After completion of treatment patients were followed up with a clinical examination and serum CEA every 3 months for 2 years and 6 monthly thereafter. In cases where there was raised CEA or any symptoms suggestive of recurrence a CECT abdomen and thorax was acquired to confirm the status of patient. LARS score was evaluated using the LARS scoring system at a median follow-up of 5 years.[9] It was categorised into major LARS (score 30-42), Minor LARS (score 21-29) and No Lars (score 0-20).

Statistical analysis

To evaluate the clinical demographic traits, surgical results, pathological staging, toxicity profiles and outcomes between the various therapy groups, statistical analysis was carried out. The statistical significance of observed changes was assessed using p-value calculations, where a p-value of less than 0.05 was deemed significant. Survival (Disease free survival [DFS] and Overall Survival [OS]) rates were estimated using the Kaplan-Meier method and compared using a stratified log-rank test. All analyses were done using SPSS statistics version 20.

Each of the high-risk features (HRF) like age <45, T4, node positive, signet ring histology, length of disease >6 cm, MRF involvement were assigned one point. Three risk categories were created: low risk (one HRF), Intermediate risk group (2-4 HRF) and high-risk group (5 or more HRF) to develop a simple risk calculator to evaluate their significance in deciding DFS and OS. Propensity score matching was done to eliminate any bias of results between the treatment arms and time-to-event analysis was performed using the Kaplan-Meier method with the log-rank test.

Results

Out of 345 patients registered, complete information regarding demographics and treatment was available for 164 patients only (fig 1). The median age was 45 years (IQR 30-57years). Other demographic features were: comorbidities in 9.7%, tumor location: upper third (14.6%), middle (third 20.7%), and lower third (64.7%), tumor length ≤6 cm (56%) and ≥6 cm (44%), mesorectal fascia (MRF) involvement (42%), T stage T3 (76.2%) and T4 (20.7%), N stage: N0 (17.1%), N1 (46.9%), and N2 (36%). Histopathological analysis classified the tumors as adenocarcinoma (78.7%), mucinous adenocarcinoma (10.4%), and signet ring cell carcinoma (10.9%). Based on the risk stratification 16% patients were in low-risk group, 72% in intermediate risk group and 12% in high-risk group. Based on age, young patients had few proportions in low risk (18%), 60% intermediate, and 89% were high risk as compared to older patients which were 30% low risk, 60% intermediate, and 4% high risk (p=0.001).

Eighty-seven patients received LCRT, 51 SCRT and 26 received only CT or no treatment due to advanced disease. The only significant toxicity due to SCRT and LCRT was grade 3 anaemia in 12% and 22% respectively, (Table 2).

Among 59 patients who underwent surgery (Table 3), R0 resection was achieved in 85% and R1 resection in 15%. The types of surgery performed included LAR (44%), ULAR in 3.4%, APR in 45.8%, and exploration and debulking in 1.7%. The major reasons for low compliance for surgery were advanced disease leading to metastases (18%), Covid (10%), complications due to CT or CTRT (7%), lost to follow-up (7%), other causes like lack of funds, co-morbidity, incomplete treatment, unwillingness for surgery were also responsible (5%). 42 patients (48.2%) did not undergo surgery in LCRT, out of which 8 (9%) are alive without disease, 3 LFU and 31 died due to an event. In SCRT arm 36 (71%) did not undergo surgery out of which 3 (6%) are alive without disease, 7 are LFU

and 26 had an event. Postoperative complications were witnessed by 20% patients undergoing APR and 15% patients undergoing LAR. The major surgical complications were infection, subacute intestinal obstruction and perineal wound infection (in patients undergoing APR).

Toxicity	**Grade**	**SCRT**	**LCRT**
		N (%)	**N (%)**
Anemia	Grade 1,2	10 (19%)	37 (42%)
	Grade 3,4	6 (11.7%)	19 (21.8%)
Neutropenia	Grade 1,2	0 (0%)	5 (5.7%)
	Grade 3,4	1 (1.9%)	3 (3.4%)
Thrombocytopenia	Grade 1,2	3 (5.8%)	5 (5.7%)
	Grade 3,4	0 (0%)	0 (0%)
Diarrhoea	Grade 1,2	2 (3.9%)	3 (3.4%)
	Grade 3,4	1 (1.9%)	3 (3.4%)
Skin reaction	Grade 1,2	2 (3.9%)	19 (21.8%)
	Grade 3,4	0 (0%)	2 (2.2%)
Nausea	Grade 1,2	4 (7.8%)	5 (5.7%)
	Grade 3,4	0 (0%)	0 (0%)

Table 2: Chemoradiation induced toxicities.

			LCRT	**SCRT**	**p value**
		n=59 (%)	**n=44 (%)**	**n=15 (%)**	
Resection	R0	50 (84.7%)	39 (88.6%)	11 (73.3%)	0.2
	R1	9 (15.3%)	5 (11.4%)	4 (26.7%)	
Type of surgery	LAR	26 (44%)	20 (45.4%)	6 (40%)	0.3
	ULAR	2 (3.4%)	1 (2.3%)	1 (6.7%)	
	APR	27 (45.8%)	21 (47.7%)	6 (40%)	
	Exploration and debulking	1 (1.7%)	0 (0%)	1 (6.7%)	
	Colostomy only	2 (3.4%)	1 (2.3%)	1 (6.7%)	
	Exenteration	1 (1.7%)	1 (2.3%)	0 (0%)	
Pathological T	T0	7 (11.9%)	6 (13.6%)	1 (6.7%)	0.7
	T1	2 (3.4%)	1 (2.3%)	1 (6.7%)	
	T2	11 (18.6%)	7 (15.9%)	4 (26.6%)	
	T3	33 (55.9%)	25 (56.8%)	8 (53.3%)	
	T4	6 (10.2%)	5 (11.4%)	1 (6.7%)	
Pathological N	N0	44 (74.6%)	32 (72.7%)	12 (80%)	0.7
	N1	13 (22%)	10 (22.7%)	3 (20%)	
	N2	2 (3.4%)	2 (4.6%)	0 (0%)	

Table 3: Surgical details (n=59).

The pathological T staging showed ypT0 (pathological CR, pCR) in 11.8%, T1 in 3.3%, T2 in 18.6%, T3 in 55.9% and T4 in 10.1%. Pathological N staging indicated ypN0 in 74.6%, ypN1 in 22%, and ypN2 in 3.4%.

At a median FU of 15 months (IQR 7-37 months), the median OS and DFS with SCRT and LCRT was 20 and 34 months and 10 and 20 months respectively. Univariate analysis for overall survival revealed that radiation type (SCRT vs LCRT, p = 0.001), tumor length ≤6 cm (p= 0.002), MRF involvement (p= 0.002), node positivity (P=0.01) was significant (Table 4). The 5-year OS of LCRT was 42% and SCRT was 25% (p=0.001) (Figure 2a,2b). Based on number of HRF, patients in high-risk group had a median OS of 11 months versus 18 months in intermediate risk group and 36 months in low-risk group (p<0.001). Cox regression analysis for OS revealed type of RT (SCRT vs LCRT) (HR 273, 95%CI 12-1753, p= 0.001) and yp node positivity as most significant factors affecting OS (HR 2.9, 95% CI 1.3-6.3, p= 0.006) (Table 5).

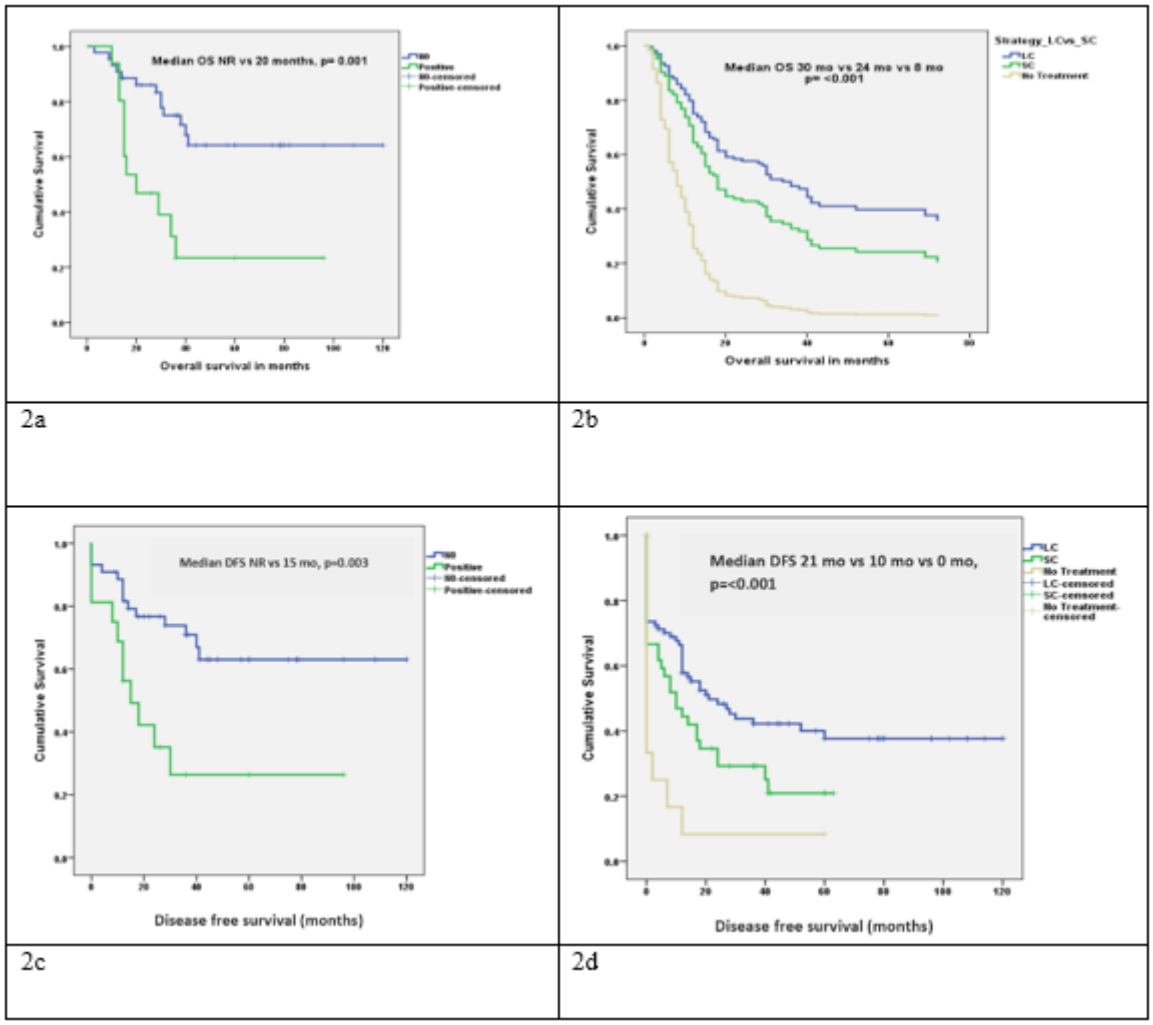

Figure 2: Kaplan Meier curves showing the overall survival (OS) (2a and 2b) and disease-free survival (DFS) for influence of node positive disease and type of RT (2c and 2d).

		number of patients		Overall Survival (months)	p value
Site	Upper 1/3rd	n=164	24 (14.6%)	17	0.54
	Middle 1/3rd		34 (20.7%)	20	
	Lower 1/3rd		106 (64.7%)	30	
MRF	Involved		69 (42%)	17	0.002
	Not involved		95 (58%)	36	
Length	≤ 6 (n=92)		92 (56%)	40	0.002
	≥ 7		72 (44%)	15	
Clinical T	T3		125 (76.2%)	30	0.06
	T4		34 (20.7%)	15	
Clinical N	Node positive		136 (82.9%)	30	0.6
	Node negative		28 (17.1%)	20	
Age	< 45		87 (53%)	18	0.12
	>45		77 (47%)	36	
Comorbidities	Present		16 (9.7%)	30	0.8
	Absent		148 (90.3%)	18	
Sex	Male		109 (66.5%)	20	0.77
	Female		55 (33.5%)	31	
Type of RT	SCRT		51 (31%)	20	0.001
	LCRT		87 (53%)	34	
Pathological T	T0	n=59	7 (11.9%)	Not reached	0.08
	T1		2 (3.4%)	Not reached	
	T2		11 (18.6%)	15	
	T3		33 (55.9%)	40	
	T4		6 (10.2%)	13	
Pathological N	Node Positive		15 (25.4%)	Not reached	0.01
	Node Negative		44 (74.6%)	20	

Table 4: Univariate analysis for overall survival (OS).

	Significance	Hazard ratio	Confidence interval
yP Node positive vs Negative	0.006	2.9	1.3 – 6.3
SCRT vs LCRT	0.001	273	12 - 1753

Table 5: Factors affecting Overall survival: cox regression analysis.

Univariate analysis for DFS revealed that MRF involvement (p value – 0.003), tumor length greater than 6 cm (p value – 0.018), higher clinical tumor stage (0.06), and type of radiotherapy (SCRT vs LCRT, p value 0.003) are important predictors (Table 6). Patients in high-risk group had a median DFS of 0 months versus 9 months in intermediate risk group and 20 months in low-risk group (p<0.001). The 5-year DFS of LCRT was 40% and SCRT was 20% (p=0.001) (Figure 2c,2d). On Cox regression analysis ypN positive status (HR 2.9,95% CI 1.2--6.9, p=0.01), and type of RT (SCRT vs LCRT, HR 29 [95% CI 3.9-213, p=0.001) were retained as significant factors (Table 7).

		number of patients		Overall Survival (months)	p value
Site	Upper 1/3rd	n=164	24 (14.6%)	7	0.59
	Middle 1/3rd		34 (20.7%)	12	
	Lower 1/3rd		106 (64.7%)	14	
MRF	Involved		69 (42%)	10	0.018
	Not involved		95 (58%)	24	
Length	≤ 6 (n=92)		92 (56%)	24	0.003
	≥ 7		72 (44%)	4	
Clinical T	T3		125 (76.2%)	17	0.06
	T4		34 (20.7%)	5	
Clinical N	Node positive		136 (82.9%)	14	0.66
	Node negative		28 (17.1%)	12	
Age	< 45		87 (53%)	8	0.24
	>45		77 (47%)	17	
Comorbidities	Present		16 (9.7%)	15	0.45
	Absent		148 (90.3%)	12	
Sex	Male		109 (66.5%)	12	0.4
	Female		55 (33.5%)	15	
Type of RT	SCRT		51 (31%)	10	0.001
	LCRT		87 (53%)	21	
Pathological T	T0	n=59	7 (11.9%)	Not reached	NA
	T1		2 (3.4%)	Not reached	
	T2		11 (18.6%)	Not reached	
	T3		33 (55.9%)	Not reached	
	T4		6 (10.2%)	Not reached	
Pathological N	Node Positive		15 (25.4%)	15	0.003
	Node Negative		44 (74.6%)	Not reached	

Table 6: Univariate analysis for disease free survival (DFS).

	Significance	Hazard ratio	Confidence interval
yP Node positive vs ypN Negative	0.01	2.9	1.2 – 6.9
SCRT vs LCRT	0.001	29	3.9 – 213

Table 7: Factors affecting Disease free survival: Cox regression analysis.

Propensity score matching was done by matching T and N status in both groups (LCRT and SCRT) as these are the important factors affecting patient survival and recurrence. On matching with a maximum tolerance of 0.05 (51 cases of LCRT were matched with 51 cases of SCRT). The median OS and DFS with SCRT and LCRT was 20 months versus 40 months and 10 months versus 52 respectively (p=0.01 and 0.002) (Figure 3a,3b).

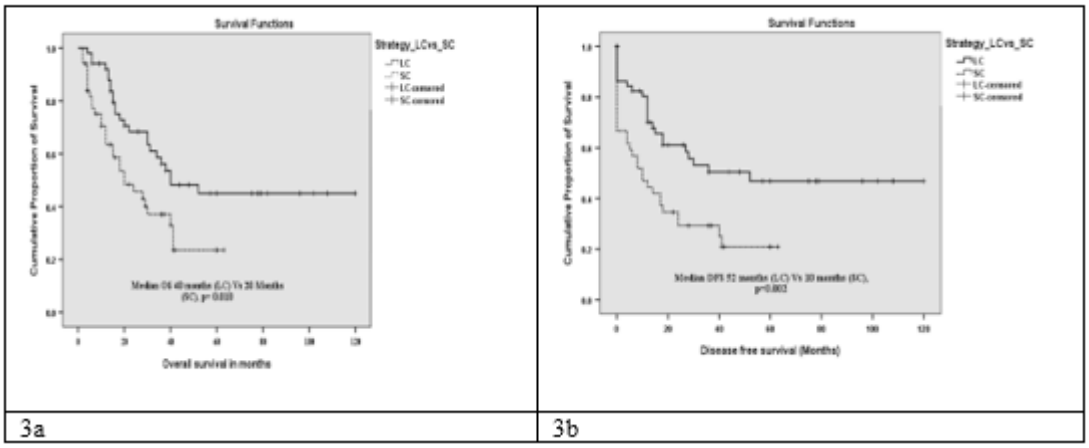

Figure 3: Kaplan Meier curves showing the overall survival (OS) (3a) and disease-free survival (DFS) (3b) after propensity score match.

We obtained information about outcomes on phone in those who did not comply to intended follow-up, so patterns of failure data were not available for all patients, hence it is not being reported here. For such patients mode of death was ascertained by symptoms at time of death. Twenty-five survivors were evaluated in May 2024 for LARS (Table 8). LCRT had a greater incidence of major LARS than SCRT, but the difference is not statistically significant.

	Major LARS	Mnior LARS	No LARS	LARS symptoms
LCRT	4 (2.4%)	1 (0.6%)	13 (7.9%)	18 (10.9%)
SCRT	0	0	7 (4.3%)	7 (4.3%)

Table 8: Distribution of LARS in rectal patients treated with LCRT and SCRT (n=25).

Discussion

The ASCO practice guidelines advocates LCRT with consolidation CT for locally advanced rectal cancer.4 In LMIC the incidence of high-risk rectal cancer is high, which comprises of young age (35%), 80% stage 2,3, lower third rectal tumours (60%), node positive (87%) and metastatic disease at presentation in one third patients.[10, 11, 12] Our data reveals that approximately 50% patients were not suitable for radical treatment and the rest 50% with available records had high risk rectal cancer. The high-risk features (HRF) in our study comprised of patients with lower third tumours (65%), more than 6 cm length of tumour (44%), MRF involvement (42%), T3 (76%) and T4 (21%), node positive in 83% and young age (<45 years) in 55% patients. These high-risk patients are best treated with TNT, but these concepts were evolving during the period of audit, when only few cycles of induction CT was administered prior to CTRT due to waiting list for RT. Our real-world data confirms that LCRT yields outcomes superior to SCRT with the overall survival and disease-free survival in LCRT being 22 and 21 months versus 15 and 10 months with SCRT with better outcomes on propensity score matching. Our 3-year DFS of 47% with LCRT is lower than 58% reported in a real-world data from Turkey, [13] and 75% reported in PRODIGE-23, 2 implying that there is a need to intensify induction CT (FOLFIRINOX instead of CAPOX in fit patients without co-morbidities and in non-elderly) to improve outcomes. The median number of CT cycles prior to CTRT was 2 in our study, which also needs to be escalated to 8-12 cycles to increase downstaging and increase in pathological complete response rates, organ conservation rates and OS. Though consolidation CT has been found to be more beneficial than induction CT in improving pCR rates and organ conservation rates, long waiting lists for RT in LMIC favours practice of induction CT rather than consolidation CT. The five-year OS results from LMIC have been reported to be as low as 29% by the CONCORD study which is primarily due to limited resources and inadequate health infra-structure.[14] Since our population had high proportion of unresectable disease and lower third rectal cancer, it resulted in poorer outcomes with SCRT as compared to data from landmark trials comparing LCRT versus SCRT in resectable disease where

the outcome of both were similar. In the unresectable patients, intensification of CT known as TNT has been reported by the POLISH,[15,16] and RAPIDO,3 studies. They demonstrated similar OS and PFS with SCRT and consolidation CT versus LCRT, while the PRODIGE-23,2 demonstrated superior OS, pCR and DFS with FOLFIRINOX induction CT followed by LCRT. At 3 years, the rates of overall survival ranged from 73% to 76% and the DFS ranged from 76% to 52%. Since we gave a median of 2 cycles induction CT prior to LCRT, our results were clearly inferior. The other reason for poor outcome in our study is that 50% of the population was less than 45 years where the OS was found to be 18 months as compared to 36 months in patients more than 45 years. Similar observations of poor outcome in young patients have been reported earlier and has been attributed to high incidence of signet ring histology as well as different biology in this subset.[11,12] Early onset Rectal Cancer (EORC) is considered a separate entity with poor biology. We took a cut off of 45 years for EORC because the median age of our population was 45 years and some studies have also taken 40 years as cutoff for EORC.[11] Westernised diet, obesity, antibiotic use, alteration of microbiome has been found to be causative factors for EORC. Although some genetic sequence variation differences have been observed between early-onset and late-onset disease, unique molecular or gene expression signatures to guide personalized treatment have not yet been identified. Younger patients typically present with more advanced disease stage and worse pathological features. In our study EORC had significantly higher proportion of HRF as compared to older population and the DFS and OS of young patients is significantly worse than that of patients more than 45 years. Social and economic factors also influence availability and timely access to healthcare in LMIC. There is also the possibility of delayed diagnosis especially in younger patients where there is lesser suspicion of a malignancy and possibility of misdiagnosis as hemorrhoids /fissures. Lack of screening programmes in LMIC also leads to presentation of patients in advanced stage which needs to be implemented by policy makers for improvement in outcomes. High stage tumours are accompanied with tumour inflammation leading to poor outcomes.[17] Inflammation accompanied with malnutrition adds to poor outcomes as almost 90% of the patients are malnourished at presentation in LMIC.[18] The incidence of signet ring histology of 10% in our patients is similar to that reported by other centres in the country.[19]

The significant factors affecting OS and DFS were length of tumour, MRF involvement, clinical T status, pathological tumour and nodal status. Pathological T and N status has been found to be a surrogate for DFS and OS in other studies as well and a better risk calculator than neoadjuvant rectal score for patients treated with LCRT. [20] The incidence of pCR was also higher in our series with LCRT (7%) than SCRT (2%) suggesting that LCRT plays a far better role in tumour downstaging than SCRT in LACR. All patients with pCR are alive which reaffirms the role of LCRT for downstaging of unresectable and lower third tumours to improve pCR.[20] We achieved 9% unintended organ conservation with LCRT and 2% with SCRT in patients who wilfully did not undergo surgery. If we combine pCR rate with organ conservation (unintended) proportions in the present study then the actual proportion of pCR with LCRT is 16% with LCRT and 4% with SCRT. Similar pCR rates have been reported in large Dutch series.[20] Patients with a pathological CR tend to achieve good DFS and OS rates and a low local recurrence rate which was observed in our study also. [21, 22] The results of our study are suboptimal and has tremendous scope for improvement in form of TNT and dose escalation. The higher response rates associated with TNT has created opportunities to preserve the rectum in more patients with LARC. [23, 24, 25,26] Based on a meta-analysis, dose escalation in such high-risk cases reported that doses above 54 Gy is associated with high rates of pCR and did not seem to increase the risk of acute grade ≥3 toxicity events. pCR rates approaching 25% may be achievable utilising moderate escalation (54-60 Gy) with modern inverse-planning techniques [27].

We developed a simple risk score to predict OS and FDS based on number of HRF. It clearly distinguishes OS and DFS in LARC based on number of HRF and can be readily used in the clinic. This risk score needs to be validated in large data bases. Since only 43% patients underwent surgery, ypT and ypN status was not incorporated in the risk scoring system. The other risk calculators are neoadjuvant rectal score which was based on cT, pT and pN status but was found to be irrelevant in large databases. Another nomogram is also available but it needs to be referred to in the clinic.

Surgical outcomes

Only 43% patients underwent surgery after neo-adjuvant CTRT. The incidence of patients undergoing surgery was higher with LCRT (50%) versus SCRT (29%). In those who underwent surgery, the incidence of R0 resection was higher with LCRT (88%) than SCRT (73%) and these rates are comparable to the literature. The incidence of sphincter preservation was similar with LCRT (48%) and SCRT (47%) but these rates are lower than those of west (84%) and high-volume centres in our country (58%). [2 ,12] The low rates of sphincter preservation in our series are because of the prevalence of lower third rectal cancer, T4 disease and EORC.

We faced challenges in the compliance to surgery due to advanced disease and HRF leading to metastases in 18% patients, again reiterating the fact that intensification of chemotherapy prior to CTRT should be adopted in routine practice. Covid was another reason for poor surgical compliance in 10% patients. Adverse

events due to CT/CTRT leading to complications and lost to follow-ups were also responsible for non-compliance to surgery in 7% and 7% patients respectively. Adverse events are more likely to occur in malnourished patients with inflammation. Out-of-pocket expenses by patients and catastrophic expenditure is common in LMIC. It has been reported that 9.4% patients have treatment attrition due to catastrophic expenditure which leads to the majority declining treatment or opting for alternative medicine, or denying treatment due to inability to pay, inability to travel or other reasons.[28] Financial constraints of patients' needs to be taken care of by a universal governmental health insurance policy. Adoption of staging PET in patients with T4 disease to rule out metastatic disease will upstage patients requiring palliative intent treatment only.[29] Patients with raised CEA prior to CTRT should also be considered for PET-CT to rule out metastatic disease.

Postoperative complications were witnessed by 20% patients undergoing APR and 15% patients undergoing LAR. The major surgical complications were infection, subacute intestinal obstruction and perineal wound infection (in patients undergoing APR) (Table 9).

	Total n (%) of complication	APR	LAR	ULAR
Surgical site infection	9 (15.2%)	3 (5.1%)	5 (8.5%)	1 (1.9%)
Subacute intestinal obstruction	9 (15.2%)	5 (8.5%)	4 (6.8%)	-
Urine retention	6 (10.2%)	4 (6.8%)	2 (3.4%)	-
Perineal wound infection	4 (6.8%)	4 (6.8%)		-
UTI	4 (6.8%)	2 (3.4%)	1 (1.9%)	-
Stoma oedema	2 (3.4%)	1 (1.9%)		-
Ureteric injury	1 (1.9%)		1 (1.9%)	-
Bleeding	1 (1.9%)	1 (1.9%)		-
Hypotension	2 (3.4%)	1 (1.9%)	1 (1.9%)	-
Anastomotic leak	1 (1.9%)	-	1 (1.9%)	-
Pelvic fluid collection	1 (1.9%)	-	-	-

Table 9: Post operative complications (n=59).

Low Anterior Resection Syndrome (LARS) is a typical after effect of low anterior resection (LAR) surgery for rectal cancer. The diseased portion of the rectum is removed in LAR, but the anal sphincter is left in place. According to a recent meta-analysis by Croese et al, 7 41% of people were thought to have LARS. Many patients who have LARS experience a considerable reduction in quality of life. To reduce symptoms and enhance results, early detection and thorough management like dietary adjustments, medication, pelvic floor therapy, and supportive care are crucial.[30] In present study, the incidence of LARS in LCRT is 10.9% versus is 4.3% in SCRT.

Limitations

The limitations of this study are that this is a retrospective analysis which has its inherent limitations. Since only 45% patients underwent surgery, ypT and ypN status was not incorporated in the risk scoring system. Secondly patterns of failure data were not available for all patients, hence the impact of LCRT on local recurrence and distant metastases could not be evaluated.

Conclusion

This real-world data shows that in a LMIC setup, one third patients present in too advanced stage not suitable for radical treatment. The rest two thirds are predominantly T3, T4, node positive with presence of HRF in 90% patients. LARC treated with LCRT showed significant improvement in overall survival compared to SCRT. The risk score postulated by us is simple and needs validation before its use in the clinic. Our findings offer valuable insights regarding outcomes with LCRT and SCRT in LMIC and help clinicians set clear expectations when counselling patients.

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