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Impact of Long-Course Neoadjuvant Radiation on Postoperative Low Anterior Resection Syndrome and Quality of Life in Rectal Cancer: Post Hoc Analysis of a Randomized Controlled Trial

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ABSTRACT

Background. Neoadjuvant radiation is recommended for locally advanced rectal cancer, with proven benefit in local control but not in disease-free survival. However, the impact of long-course radiation on postoperative bowel function and quality of life (QOL) remains controversial. This study aimed to investigate the impact of long-course neoadjuvant radiation on bowel function and QOL, and to identify risk factors for severe bowel dysfunction.

Methods. Patients who underwent long-course neoadjuvant chemoradiotherapy (nCRT) or chemotherapy (nCT) followed by radical low anterior resection for locally advanced rectal cancer were recruited from the FOWARC randomized controlled trial. Low anterior resection syndrome (LARS) score and European Organisation for Research and Treatment of Cancer (EORTC) C30/CR29 questionnaires were used to assess bowel function and QOL, respectively.

Results. Overall, 220 patients responded after a median follow-up of 40.2 months, of whom 119 (54.1%) reported major LARS, 74 (33.6%) reported minor LARS, and 27 (12.3%) reported no LARS. Compared with the nCT group, the nCRT group reported more major LARS (64.4% vs. 38.6%, $p < 0.001$) and worse QOL. Long-course neoadjuvant radiation (OR 2.20, 95% CI 1.24–3.91; $p = 0.007$), height of anastomosis (OR 0.74, 95% CI 0.63–0.88; $p < 0.001$), and diverting ileostomy (OR 2.59, 95% CI 1.27–5.30; $p = 0.009$) were independent risk factors for major LARS.

Conclusions. Long-course neoadjuvant radiation, along with low anastomosis, are likely independent risk factors for postoperative bowel function and QOL. Our findings might have implications for alleviating LARS and improving QOL by informing selection of neoadjuvant treatment.

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Oncological outcomes of rectal carcinoma have improved markedly thanks to total mesorectal excision (TME) and multidisciplinary treatment.[1,2] The advancement of anastomotic techniques has made sphincter-preserving low anterior resection (LAR) possible in the majority of cases, without hampering oncological control.[3–5] However, symptoms associated with bowel movements have been reported,[6] including fecal or flatus incontinence, frequent bowel movements, clustering, and urgency, which are collectively defined as low anterior resection syndrome (LARS).[7] Approximately 70–90% of patients are reported to experience some extent of LARS, and some suffer major LARS with poor quality of life (QOL) for many years.[6]

Although neoadjuvant chemoradiotherapy (nCRT) combined with TME is the current standard treatment for locally advanced rectal carcinoma, adverse effects of radiotherapy on postoperative bowel function and QOL have been documented.[8] This negative functional impact of neoadjuvant radiation is contrasted with the failure to translate its gain in local control into overall survival.[1,9] Mechanisms of radiation affecting bowel movement have been suggested, including nerve damage, impairment of the anal sphincter, and decreased neorectal compliance caused by radiation-induced fibrosis.[6,10–13] However, reported studies are mostly retrospective with factors confounding the effect of radiation, or focused on short-course radiation. Moreover, most authors used fecal incontinence instruments while omitting other symptoms that impair QOL.[14] In this study, LARS score and QOL questionnaires were used in the setting of FOWARC, a randomized controlled trial, to investigate more vigorously the functional impact of long-course neoadjuvant radiation.[15]

METHODS

Patients and Characteristics

Patients were recruited from a single-center cohort of the randomized, phase III FOWARC trial as previously described (NCT01211210).[15] Briefly, patients with stage II or III rectal adenocarcinoma were randomized to receive neoadjuvant (1) fluorouracil plus radiotherapy, (2) mFOLFOX6 (modified fluorouracil, leucovorin, and oxaliplatin) chemotherapy plus radiotherapy, or (3) mFOLFOX6 alone, before undergoing TME resection and adjuvant chemotherapy, from 2010 to 2015. A radiation dose of 46.0–50.4 Gy was delivered in 23–28 fractions to the primary tumor and to mesorectal, presacral, and internal iliac lymph nodes. A protective diverting stoma was constructed at the surgeon's discretion. Anastomotic leak was defined as communication between the intra- and extraluminal compartments.[16] Clinically symptomatic leak was confirmed by pus or fecal discharge from the pelvic drain, computed tomography (CT), magnetic resonance imaging (MRI), colonoscopy or re-laparotomy. In addition, we routinely perform defecography before reduction of ileostomy (3 months after surgery, if applicable), as well as CT, during the 6-month postoperative follow-up, to detect any subclinical leak. Demographic and clinical characteristics of patients were obtained from the colorectal cancer database of the Sixth Affiliated Hospital, Sun Yat-sen University. Distances of tumor and anastomosis from the anal verge were measured using MRI, digital rectal examination, and colonoscopy. Patients who suffered recurrence or metastasis were subsequently excluded in the analysis of QOL. All participants provided written informed consent. This study was approved by the Medical Ethics Committee of the Sixth Affiliated Hospital, Sun Yat-sen University.

Quality of Life (QOL) and Low Anterior Resection Syndrome (LARS) Questionnaires

The LARS score, a valid and reliable scoring system correlated to QOL, was applied to assess postoperative bowel movement dysfunction.[7,17,18] Five items, i.e. incontinence of flatus, incontinence of liquid stool, frequency of bowel movements, clustering of stools, and urgency, total 0–42 points. According to its correlation with QOL, the LARS score is graded into three levels: (1) no LARS (0–20 points); (2) minor LARS (21–29 points); and (3) major LARS (30–42 points).[7] Patients with missing items in the LARS score were excluded from the analysis, while patients with tumor recurrence or distant metastasis were included, considering its little effect on LARS.

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core Questionnaire (QLQ-C30) Version 3.0 comprises 30 questions corresponding to five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single-item questions (constipation, diarrhea, loss of appetite, insomnia, dyspnea, and financial difficulties), and a global health status.[19] The colorectal cancer-specific EORTC QLQ-Colorectal Cancer Module (CR29) questionnaire consists of 29 questions evaluating the colorectal cancer-specific symptom and functional scales.[20] Stoma-related scales of the QLQ-CR29 module were excluded.

The QOL scores and missing data were handled according to the EORTC scoring manual. Scales with at least 75% of the items completed were considered available, and the missing item(s) were imputed by the mean of the items present. All scales and single-item raw scores were linearly transformed to scores ranging from 0 to 100

points. A high global health status score represents a high QOL, while a higher functional score represents better function (optimal score, 100), and a higher symptom score represents worse symptoms (optimal score, 0). QOL data are presented as mean with standard deviation (SD), as recommended by the EORTC.[19] Clinical significance of QOL score differences were defined as none ($\leq$ 5.0), minor (5.1–10.0), moderate (10.1–20.0), or large ($>$ 20.0).[21]

In mid 2017, eligible patients were contacted by telephone to complete the questionnaires during a regular visit to the clinic or via mail. If response questionnaires contained missing item(s), we reconfirmed via telephone or resent the questionnaires. Patients with no response were contacted every 3 weeks by telephone, and those who made no response by 12 weeks were defined as non-responders.

Statistical Analysis

Patients treated with fluorouracil plus radiation or mFOLFOX6 plus radiation had comparable clinical characteristics, severity of LARS, and QOL (electronic supplementary Tables 1–3). Thus, we combined the two groups into one nCRT group, compared with the neoadjuvant chemotherapy (nCT) group receiving mFOLFOX6 alone. For our first primary hypothesis that nCRT might be associated with more severe LARS, we used a logistic regression model to test the association of neoadjuvant radiation (a binary predictor variable) with LARS severity (an ordinal outcome variable). To control for confounding, a multivariate logistic regression model initially included 11 clinical characteristics, i.e. age at proctectomy (continuous), sex, body mass index (BMI; continuous), time since proctectomy (continuous), clinical tumor, node, and metastasis (cTNM) staging at diagnosis (II/III), distance from the distal tumor edge to the anal verge (continuous), height of anastomosis (continuous), anastomotic leak, diverting ileostomy, time between ileostomy construction and reversal (continuous), and time between completion of radiation and proctectomy (continuous). A backward stepwise elimination with a threshold of $p = 0.05$ was used to select covariates in the final models.

All other analyses were secondary exploratory analyses. For associations of the 11 clinical characteristics and the five LARS symptoms with neoadjuvant radiation, we adjusted the two-sided α level to 0.003 [= 0.05/(11 + 5)], by simple Bonferroni correction for multiple comparisons. To compare continuous data between neoadjuvant therapy (nCRT vs. nCT), the Mann–Whitney *U* test was performed, and to compare categorical data, the Chi-square test or Fisher's exact test was performed. SPSS version 23.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. All *p* values were two-sided and a p value < 0.05 was considered statistically significant unless stated otherwise.

RESULTS

Patient Characteristics

A total of 327 patients were enrolled at the Sixth Affiliated Hospital, Sun Yat-sen University. Ninety-two patients were excluded due to death ($n = 30$), undergoing non-LAR surgery ($n = 39$) or no surgery ($n = 9$), and persistent stoma or reoperation with permanent stoma ($n = 14$). Fifteen of the remaining 235 patients declined participation or made no response, leaving 220 patients for final analyses (Fig. 1). No statistically significant differences were found for the clinical characteristics between participants and non-participants (electronic supplementary Table 4). Baseline data of QOL and bowel function were comparable between treatment arms (electronic supplementary Tables 5 and 6), and the median follow-up was 40.2 months (range 23.1–87.3). Demographic and clinical characteristics were balanced between the nCRT and nCT groups, except for diverting ileostomy (87.1% vs. 62.5%; $p < 0.001$) and anastomotic leak (16.7% vs. 6.8%; $p = 0.03$, Table 1).

LARS Score

Of all 220 patients responding to the LARS scale, 119 (54.1%) had major LARS, 74 (33.6%) had minor LARS, and 27 (12.3%) had no LARS. Patients in the nCRT group reported a higher prevalence of major LARS compared with the nCT group (64.4% vs. 38.6%; $p < 0.001$). A 5-item breakdown of LARS score showed that the nCRT group experienced worse symptoms, including incontinence of flatus, incontinence of liquid stool, frequency of bowel movement, and urgency (Table 2).

In our primary hypothesis testing, we conducted univariate and multivariate logistic regression analyses to assess the associations of neoadjuvant radiation (a binary predictor variable) with LARS severity (an ordinal outcome variable, Table 3). Neoadjuvant radiation was positively associated with LARS severity in multivariate analyses (multivariate odds ratio [OR] 2.20. 95% confidence interval [CI] 1.24–3.91; multivariate $p = 0.007$).

Association of patient characteristics with LARS severity was examined as secondary analyses, with an adjusted α level of 0.003 (Table 3). Independent risk factors for major LARS included height of anastomosis (OR 0.74, 95% CI 0.63–0.88; multivariate $p < 0.001$), and diverting ileostomy (OR 2.59, 95% CI 1.27–5.30; multivariate $p = 0.009$).

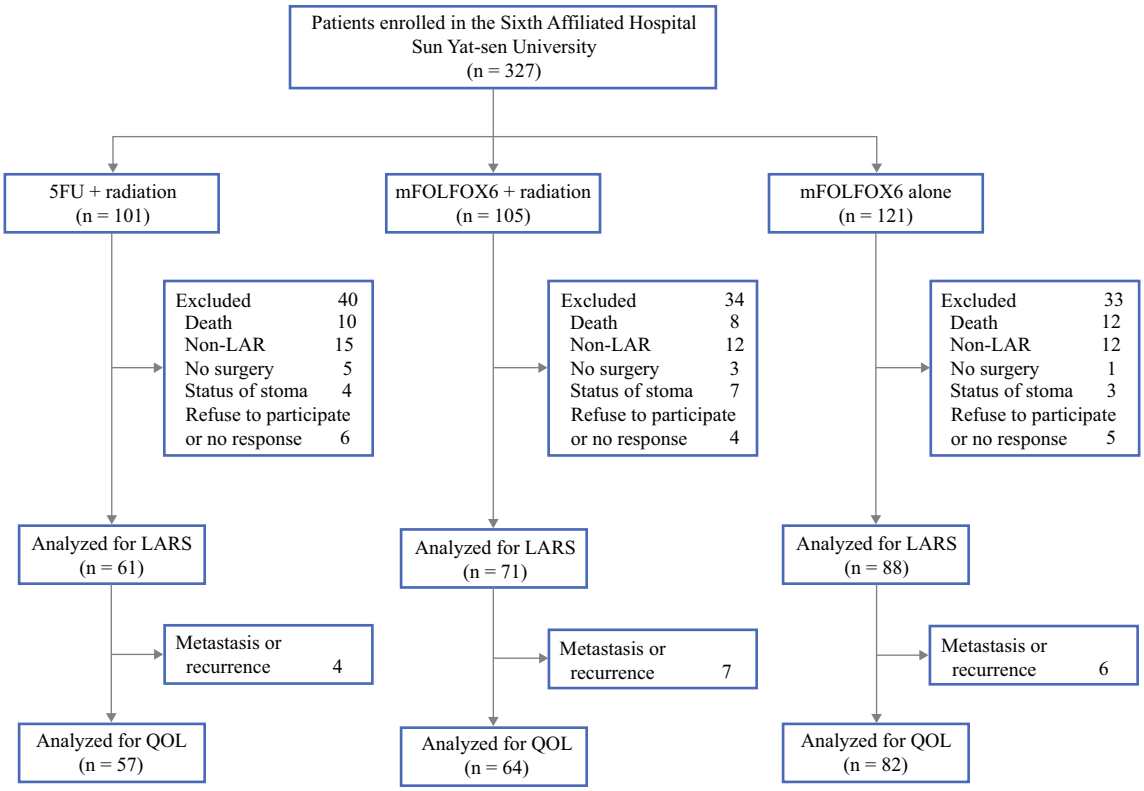

FIG. 1 CONSORT diagram of the study selection process. A total of 220 patients were analyzed for LARS, among whom 203 were analyzed for QOL. *5FU* fluorouracil, *mFOLFOX6* modified fluorouracil, leucovorin, and oxaliplatin. *LAR* low anterior resection, *LARS* low anterior resection syndrome, *QOL* quality of life

QOL

In QLQ-C30, statistically and clinically significant differences were present for global health status (6.2 points, minor), role functioning (14.1 points, moderate), and social functioning (9.3 points, minor) between the nCRT and nCT groups (Fig. 2). No statistically significant differences were found for the symptom scales.

In QLQ-CR29, statistically and clinically significant differences were detected in stool frequency (5.7 points, minor; $p = 0.009$), flatulence (11.6 points, moderate; $p = 0.003$), fecal incontinence (13.1 points, moderate; $p < 0.001$), sore skin (6.2 points, minor; $p = 0.03$), and embarrassment (12.6 points, moderate; $p < 0.001$). No statistically significant differences were found in functional scores (Fig. 3).

DISCUSSION

We conducted this study to test the hypothesis that long-course neoadjuvant radiation might be associated with worse LARS and QOL. Compared with the nCT group, patients in the nCRT group reported more severe LARS, worse QOL functional scales, and defecation-related symptoms. Multivariate analyses confirmed long-course neoadjuvant radiation, along with height of anastomosis and diverting ileostomy, as independent risk factors for major LARS.

Although a common morbidity, LARS tends to be underestimated, both in incidence and significance.[6,22,23] Various scales have been used to investigate bowel function after LAR, including the Wexner incontinence instrument.[24] However, LARS is a set of different symptoms (more than just incontinence), and has significant impact on QOL.[25–27] In this study, at a median follow-up of 37.1 months, 54% of patients reported major LARS, which is comparable with the previously reported 46–56% at least 1 year after proctectomy, when further improvement was unlikely.[22,25,28] Our study also added to the evidence that neoadjuvant radiation affects QOL by aggravating defecation-related symptoms, which overlaps with LARS, and by impairing social and role functioning.

Neoadjuvant radiation is recommended for locally advanced rectal cancer by bringing better local control,[29] which has failed to translate into improved overall survival in the TME era.[1,30,31] Meanwhile, radiation costs in function.[25,27,28] The Dutch trial showed that 14 years after surgery, patients with short-course (5×5 Gy) preoperative radiotherapy experienced major LARS more often than those without (56% vs. 36%; $p < 0.01$).[25] However, for

TABLE 1 Clinical and pathological characteristics according to treatment groups in 220 patients

Characteristics	nCRT + TME [n = 132]	nCT + TME [n = 88]	p value[a]
Age at surgery (years)	56 (27–77)	55 (21–77)	0.40
Sex			
Male	88 (66.7)	57 (64.8)	0.77
Female	44 (33.3)	31 (35.2)	
BMI	22.2 (12.8–33.2)	22.8 (15.4–34.0)	0.39
cTNM			
II	27 (20.5)	24 (27.3)	0.24
III	105 (79.5)	64 (72.7)	
Tumor height (cm)[c]			
≤ 5	52 (39.4)	29 (33.0)	0.57
5–10	73 (55.3)	55 (62.5)	
> 10	7 (5.3)	4 (4.5)	
Days from completion of radiotherapy to surgery	50 (18–150)	NA	NA
Height of anastomosis (cm)[c]	4.0 (0.5–8.0)	4.0 (1.0–12.0)	0.44
Months since primary surgery	37.1 (23.1–87.3)	42.1 (24.8–78.8)	0.06
Diverting stoma			
Yes	115 (87.1)	55 (62.5)	<0.001
No	17 (12.9)	33 (37.5)	
Months before ileostomy reversal[b]	5.2 (0.6–17.5)	5.4 (1.7–22.9)	0.64
Anastomotic leak			
Yes	22 (16.7)	6 (6.8)	0.03
No	110 (83.3)	82 (93.2)	

Data are expressed as median (range) or n (%)

nCRT neoadjuvant chemoradiotherapy, *TME* total mesorectal excision, *nCT* neoadjuvant chemotherapy, *BMI* body mass index, *cTNM* clinical tumor, node, and metastasis, *NA* not applicable

[a]To compare categorical data between treatment groups, the Chi square test or Fisher's exact test was performed, and to compare continuous data, the Mann–Whitney U test was performed. We adjusted two-sided α level to 0.003 [= 0.05/(11 + 5)] by simple Bonferroni correction

[b]Data were calculated in patients with diverting stoma

[c]The distance from the anal verge to anastomosis or inferior tumor border

long-course radiation, the evidence is limited.[30,32] Our study helps to answer this question, with a relatively large cohort in the setting of a randomized controlled trial.[15]

To our knowledge, this study is the first to report the association of low anastomosis with LARS. Although the nCRT group had a higher rate of distal cancers than the nCT group, the difference was not statistically significant (p = 0.57). Multivariate logistic regression analysis showed that height of anastomosis, rather than tumor height, was an independent risk factor for LARS. The height of anastomosis was comparable between the two groups (electronic supplementary Fig. 1), suggesting that its association with LARS was unlikely to be confounded by treatment group. For patients with low rectal cancer expecting sphincter-saving surgery, we recommend every effort be made to preserve longer distal rectal stump, in addition to abstinence from neoadjuvant radiation. However, if both radiation and low anastomosis are inevitable due to the advanced stage and/or distal location of the tumor, the probability of major LARS and QOL impact should be emphasized to enable an informed and personalized choice between bowel continuity and permanent colostomy.[33]

Diverting ileostomy has been proposed to reduce anastomotic leak after LAR,[34–36] while some argue that it merely alleviates the symptoms and consequences of leak without lowering its incidence.[37] To investigate whether the effect of radiation on LARS might be mediated by increased anastomotic leak, we compared all three groups of patients after excluding cases with anastomotic leak, and found similar differences in LARS (p = 0.005) [electronic supplementary Table 7]. Multivariate analysis excluding anastomotic leak cases also showed radiation as an independent risk factor for major LARS (multivariate p = 0.003) [electronic supplementary Table 8]. Evidence of diverting ileostomy on LARS is mixed. Previous studies

TABLE 2 Comparison of LARS score and individual LARS items between treatment groups

Item[a]	Total [n = 220]	nCRT + TME [n = 132]	nCT + TME [n = 88]	p value[b]
LARS score				< 0.001
0–20 (no LARS)	27 (12.3)	10 (7.6)	17 (19.3)	
21–29 (minor LARS)	74 (33.6)	37 (28.0)	37 (42.1)	
30–42 (major LARS)	119 (54.1)	85 (64.4)	34 (38.6)	
Incontinence for flatus				0.003
Never	98 (44.6)	49 (37.1)	49 (55.7)	
Less than once weekly	61 (27.7)	38 (28.8)	23 (26.1)	
At least once weekly	61 (27.7)	45 (34.1)	16 (18.2)	
Incontinence for liquid stool				< 0.001
Never	83 (37.7)	36 (27.3)	47 (53.4)	
Less than once weekly	62 (28.2)	39 (29.5)	23 (26.1)	
At least once weekly	75 (34.1)	57 (43.2)	18 (20.5)	
Daily frequency of bowel movement				< 0.001
> 7	25 (11.4)	21 (15.9)	4 (4.6)	
4–7	81 (36.8)	61 (46.2)	20 (22.7)	
1–3	95 (43.2)	35 (26.5)	60 (68.1)	
< 1	19 (8.6)	15 (11.4)	4 (4.6)	
Clustering				0.22
Never	2 (0.9)	1 (0.8)	1 (1.1)	
Less than once weekly	70 (31.8)	38 (28.8)	32 (36.4)	
At least once weekly	148 (67.3)	93 (70.4)	55 (62.5)	
Urgency				0.003
Never	12 (5.5)	2 (1.5)	10 (11.4)	
Less than once weekly	80 (36.4)	44 (33.3)	36 (40.9)	
At least once weekly	128 (58.1)	86 (65.2)	42 (47.7)	

Data are expressed as n (%)

LARS low anterior resection syndrome, *nCRT* neoadjuvant chemoradiation therapy, *TME* total mesorectal excision, *nCT* neoadjuvant chemotherapy

[a]Items include total LARS score and individual LARS items

[b]The Mann–Whitney U test was performed. For individual LARS items, we adjusted two-sided α level to 0.01 (= 0.05/5) by simple Bonferroni correction

desmontrated that diverting ileostomy worsened incontinence and LARS.[38,39] In contrast, Hughes et al.[28] reported no association between diverting stoma and LARS. Furthermore, Emmertsen and Laurberg[22] showed temporary stoma as a univariate risk factor for major LARS (OR 4.51. 95% CI 2.28–8.93), but not after adjustment for tumor height (OR 1.73. 95% CI 0.44–6.91). Although both tumor height and anastomotic height were comparable between the groups in our study, the choice of diverting ileostomy was arbitrary upon the surgeon's discretion, and more often in the radiation group (87.1% vs. 62.5%, $p < 0.001$). Because the confounding of diverting ileostomy by radiation is inseparable, the multivariate association of ileostomy with LARS should be interpreted with caution.

One limitation of our study is the subset analyses of the whole FOWARC randomized controlled trial.[15] Nevertheless, the analyzed subset was drawn from the largest contributing institute of the trial and had similar patient characteristics as the whole study. In addition, the breakdown of excluded cases of all causes shows comparable distribution between treatment groups (Fig. 1). Another limitation is the exclusion criteria of stoma status for the evaluation of LARS, which inevitably contained patients who had experienced severe anastomotic leak or LARS that necessitated persistent ostomy; however, this would most likely weaken our positive finding because both anastomotic leak and LARS were more common in the nCRT group.

TABLE 3 Neoadjuvant therapy, patient characteristics, and LARS score

Variable	No LARS	Minor LARS	Major LARS	Univariate analysis		Multivariate analysis[a]	
	[*n* = 27 (12.3%)]	[*n* = 74 (33.6%)]	[*n* = 119 (54.1%)]	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age at surgery (years)	58 (21–73)	51 (23–77)	57 (27–77)	1.01 (0.99–1.03)	0.24		NA
Sex					0.18		
Male	18 (12.4)	54 (37.2)	73 (50.4)	0.68 (0.40–1.19)			
Female	9 (12.0)	20 (26.7)	46 (61.3)	1			
BMI	22.6 (16.0–28.5)	22.5 (17.2–28.3)	22.5 (12.8–34.0)	1.0 (0.92–1.08)	0.99		NA
cTNM					0.88		
II	6 (11.8)	17 (33.3)	28 (54.9)	1			
III	21 (12.4)	57 (33.7)	91 (53.9)	0.96 (0.52–1.75)			
Tumor height (cm)[b]	8.2 (3.5–12.0)	7.0 (2.0–12.0)	5.7 (1.7–12.0)	0.76 (0.68–0.86)	< 0.001	0.96 (0.80–1.15)	0.63
Neoadjuvant therapy					< 0.001		0.007
nCT	17 (19.3)	37 (42.1)	34 (38.6)	1		1	
nCRT	10 (7.6)	37 (28.0)	85 (64.4)	2.88 (1.69–4.91)		2.20 (1.24–3.91)	
Days from completion of radiation to surgery[c]	51.5 (43–67)	49 (29–84)	51 (18–150)	1.01 (0.98–1.03)	0.59		NA
Height of anastomosis (cm)[b]	5.0 (2.0–12.0)	4.0 (1.0–8.0)	3.0 (0.5–8.0)	0.67 (0.58–0.78)	< 0.001	0.74 (0.63–0.88)	< 0.001
Months since primary surgery	42.5 (23.1–80.6)	38.9 (24.8–87.3)	40.2 (24.1–84.2)	0.99 (0.97–1.01)	0.33		NA
Diverting ileostomy					< 0.001		0.009
No	15 (30.0)	23 (46.0)	12 (24.0)	1		1	
Yes	12 (7.1)	51 (30.0)	107 (62.9)	5.48 (2.91–10.32)		2.59 (1.27–5.30)	
Months before ileostomy reversal[c]	5.1 (3.5–7.3)	5.2 (1.7–17.5)	5.4 (0.6–22.9)	1.01 (0.89–1.14)	0.88		NA
Anastomotic leak					0.01		0.052
No	24 (12.5)	71 (37.0)	97 (50.5)	1			
Yes	3 (10.7)	3 (10.7)	22 (78.6)	3.23 (1.29–8.11)		2.63 (0.99–6.95)	

Data are expressed as median (range) or *n* (%) unless otherwise stated

LARS low anterior resection syndrome, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *cTNM* clinical tumor, node, and metastasis, *nCT* neoadjuvant chemotherapy, *nCRT* neoadjuvant chemoradiotherapy, *NA* not applicable

[a]The multivariate ordinal logistic regression model with LARS severity as an ordinal outcome initially included neoadjuvant therapy and all 11 clinical characteristics. A backward stepwise elimination with a threshold of $p < 0.05$ was used to select variables in the final model

[b]The distance from the anal verge to anastomosis or inferior tumor border

[c]Data were calculated from 132 patients receiving nCRT, or 170 patients with diverting stoma

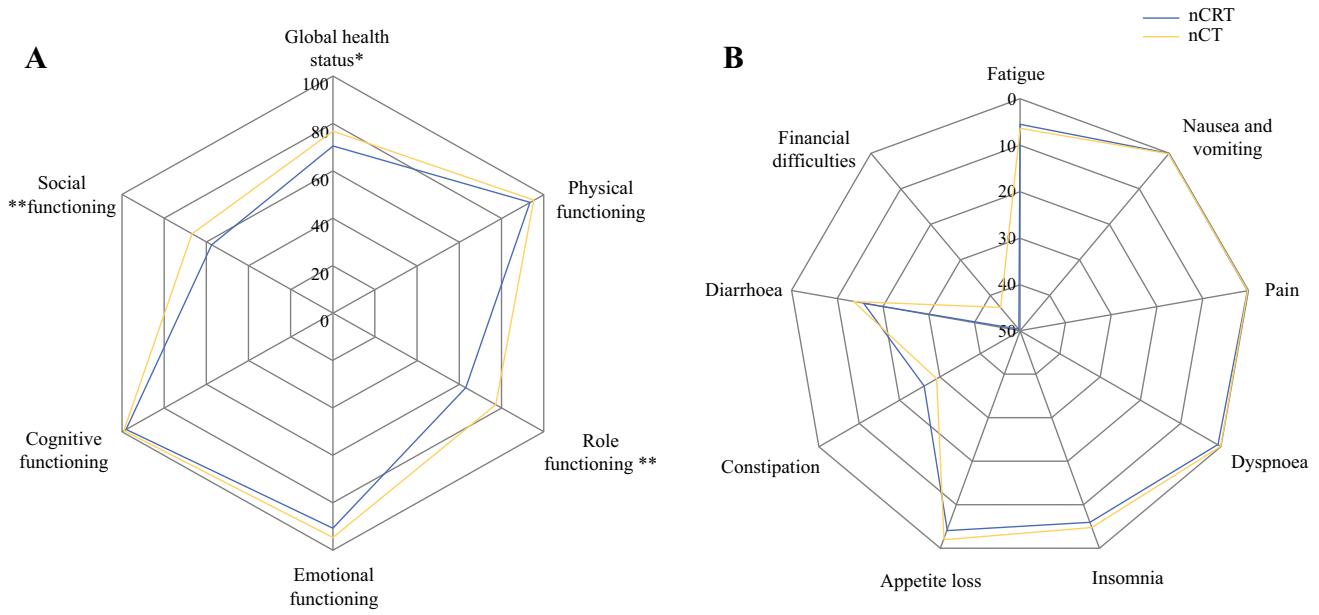

FIG. 2 Comparison of the EORTC QLQ-C30 subscales between treatment arms among patients without recurrence or metastasis (n = 203). **a** Functional scales, where a higher score means better function. **b** Symptom scales, where a higher score means worse symptoms. *$p < 0.05$ with minor clinical significance (score difference: 5–10); **$p < 0.05$ with moderate clinical significance (score difference: 10–20). *EORTC* European Organisation for Research and Treatment of Cancer, *QLQ-C30* Quality of Life Questionnaire-Core Questionnaire, *nCRT* neoadjuvant chemoradiotherapy, *nCT* neoadjuvant chemotherapy

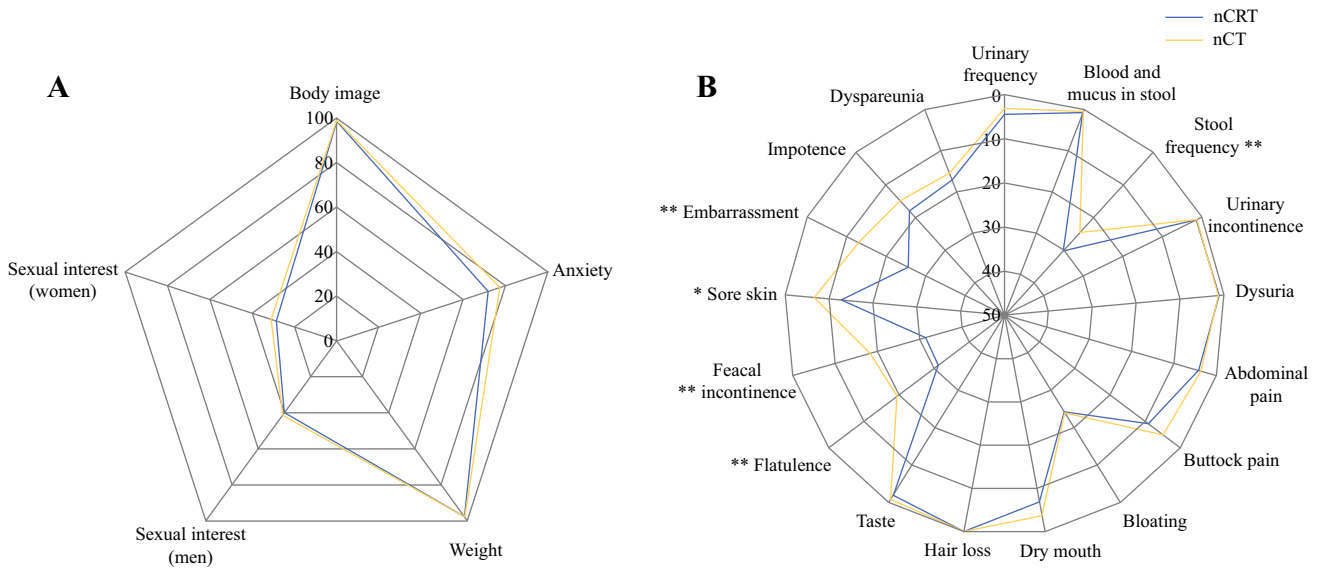

FIG. 3 Comparison of EORTC QLQ-CR29 subscales between treatment arms, among patients without recurrence or metastasis (n = 203). **a** Functional scales, where a higher score means better function. **b** Symptom scales, where a higher score means worse symptom. *$p < 0.05$ with minor clinical significance (score difference: 5–10); **$p < 0.05$ with moderate clinical significance (score difference: 10–20). *EORTC* European Organisation for Research and Treatment of Cancer, *QLQ-CR29* QLQ-Colorectal Cancer Module, *nCRT* neoadjuvant chemoradiotherapy, *nCT* neoadjuvant chemotherapy

Our study has several strengths. First, this study utilized the largest single-center subset representative of the FOWARC randomized controlled trial, which enabled us to rigorously test the association of radiation with LARS and QOL because the choice of radiation or not was randomized and thus could not be confounded. Second, our dataset integrates demographic characteristics, clinico-pathological features, complications, and related treatments. Combined with multivariate analysis and stringent statistical criteria, this allowed us to detect

potential co-risk factors for LARS for future study. Third, the simultaneous collection of LARS and QOL data in our study has demonstrated a consistent impact of radiation on both, validating LARS as a morbidity that significantly impairs the QOL of patients.

CONCLUSIONS

LARS is a common morbidity in patients with rectal cancer who undergo LAR. Long-course neoadjuvant radiation is associated with more severe LARS and worse QOL, and low anastomosis might pose additional risk for LARS. Our findings support a re-evaluation of the rationale for neoadjuvant radiotherapy. Further prospective studies are warranted to validate the effect of anastomotic height on LARS. Upon validation, these findings may have implications for alleviating LARS and improving QOL by informing treatment selection.

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