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ORIGINAL ARTICLE

Quality of life in a randomized trial comparing two neoadjuvant regimens for locally advanced rectal cancer—INCAGI004

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Abstract

Background Neoadjuvant chemoradiotherapy (neoCRT) followed by surgery is the standard of care for locally advanced rectal cancer (LARC), but the emergence of different drug regimens may result in different response rates. Good clinical response translates into greater sphincter preservation, but quality of life (QOL) may be impaired after treatment due to chemoradiotherapy and surgical side effects.

Objective To prospectively evaluate the impact of clinical response and surgical resection on QOL in a randomized trial comparing two different neoCRT regimens.

Methods Stage II and III rectal cancer patients were randomized to receive neoCRT with either capecitabine (group 1) or 5-Fu and leucovorin (group 2) concomitant to long-course radiotherapy. Clinical downstaging was accessed using MRI 6–8 weeks after treatment. EORTCs QLQ-C30 and CR38 were applied before treatment (T0), after neoCRT (T1), after rectal resection (T2), early after adjuvant chemotherapy (T3), and 1 year after the end of treatment or stoma closure (T4). The Wexner scale was used for fecal incontinence evaluation at T4. A C30SummaryScore (Geisinger and cols.) was calculated to compare QOL results.

Results Thirty-two patients were assigned to group 1 and 31 to group 2. Clinical downstaging occurred in 70.0% of group 1 and 53.3% of group 2 ($p=0.288$), and sphincter preservation was 83.3% in group 1 and 80.0% in group 2 ($p=0.111$). No significant difference in QOL was detected when comparing the two treatment groups after neoCRT using QLQ-C30. However, the CR38 module detected differences in micturition problems (15.3 points), gastrointestinal problems (15.3 points), defecation problems (11.8 points), and sexual satisfaction (13.3 points) favoring the capecitabine group. C30SummaryScore detected significant improvement comparing T0 to T1 and deterioration comparing T1 to T2 ($p=0.025$). The mean Wexner scale score was 9.2, and a high score correlated with symptoms of diarrhea and defecation problems at T4.

Conclusions QOL was equivalent between groups after neoCRT except for micturition problems, gastrointestinal problems, defecation problems, and sexual satisfaction favoring the capecitabine arm after. The overall QOL using the C30SummaryScore was improved after neoCRT, but decreased following rectal resection, returning to basal levels at late evaluation. Fecal incontinence was high after sphincter preservation.

Trial registration ClinicalTrials.gov Identifier: NCT03428529.

Keywords Rectal cancer · Quality of life · Neoadjuvant treatment · Radiotherapy · Chemotherapy · Surgical oncology

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Background

Colorectal cancer is the third most common malignant neoplasia worldwide (1.4 million new cases/year) [1]. In Brazil, it is the third most frequent cancer in men and second in women [2]. Locally advanced rectal cancer (LARC) is the denomination for tumors centered below the peritoneal reflection, usually < 10–12 cm from the anal verge (AV), and that have extended beyond the muscularis propria or the rectum (AJCC clinical stages II and III) [3]. Neoadjuvant chemoradiotherapy (neoCRT) using 5-fluorouracil and leucovorin (5-Fu/Lv) followed by total mesorectal excision (TME) is considered the standard of care for locally advanced rectal cancer (LARC) resulting in > 70% 5-year survival [4, 5]. Capecitabine is an oral substitute to 5-Fu that has been tested in neoadjuvant phase 2 trials that demonstrated superiority in clinical and pathological response rates [6, 7]. Phase 3 trials have shown comparable efficacy [8, 9]. Capecitabine has the potential advantages of synergism with radiation due to thymidine phosphorylase upregulation [10], increased concentration in colorectal tumor tissue [11], and the convenience of oral administration [12].

The adoption of total mesorectal excision (TME) [13] combined with the neoadjuvant treatment has resulted in an excellent local control, with local recurrences occurring in 3–6% of patients [5, 14]. Therefore, abdominoperineal resection, or Miles's operation [15], has been avoided progressively in favor of sphincter-preserving procedures such as low anterior resection and intersphincteric resection [16] when sufficient distal and circumferential negative margins are secured.

Besides advances in local control and sphincter preservation for LARC, quality of life (QOL) becomes a great problem after treatment due to temporary or permanent stoma creation [17], sexual and urinary dysfunction [18], and a myriad of defecation disfunctions now classified as low anterior resection syndrome (LARS) [19].

The European Organization for Research and Treatment on Cancer (EORTC) has published in 1993 a questionnaire with 30 questions, the QLQ-C30 [20], which has been extensively used to measure patient-reported outcomes in oncology for all cancer types. It displays the QOL results in 15 domains divided in five functional scales, nine symptom scales, and one global QOL scale. In rectal cancer, it is usually applied with the addition of specific colorectal modules [21, 22]. Nonetheless, QOL analysis using the multi-item scales may lead to conflicting conclusions because some symptoms may ameliorate after treatment while others may get worse. For example, some studies favor sphincter preservation [23], but others suggest equivalent or worse results when comparing patients with low rectal anastomosis with definitive stoma [24].

A summary measure to aggregate the multi-dimensional QoL profile and to detect changes in overall QOL over time is particularly important in clinical trials, which are designed to pre-specified endpoints. The original two-item global QOL scale may not be comprehensive enough to detect changes between patient groups and/or changes over time. It has been shown that the Global QOL scale could not detect deteriorating QOL in patients with progressive and terminal disease [25].

Within this scenario, a group of authors recently proposed a higher-order summary score that performed well in an empirical model fit [26]. It was calculated by the mean of all C30 scales except for the Financial Problems scale and Global QOL scale and was denominated C30 Summary Score (C30SumScore). It has been tested in a lung cancer study including 326 patients 3 months after lung resection and demonstrated better sensitivity to detect postoperative changes compared to the Global QOL scale [27]. In addition, the C30SumScore performed better than the scales of Global QOL and Physical Functioning predicting all-cause mortality in colon and rectal cancer patients [28].

In the present study, we performed a QOL evaluation in LARC patients using EORTC's QOL questionnaires QLQ-C30, CR38, and the C30SumScore to detect differences associated with the clinical response and to the surgical therapy in a randomized prospective trial comparing two different neoCRT regimens in a tertiary cancer hospital.

Objective

This study aims to prospectively evaluate the impact of clinical response and surgical resection on QOL in a randomized trial comparing two different neoCRT regimens.

Methods

Study design

This was a longitudinal prospective study approved by the Ethics Committee of the National Cancer Institute of Brazil (INCA) in 2010 under registration number 83/10 (NCT03428529). Patients were randomized to receive neoCRT using either capecitabine or bolus 5-Fu/Lv concomitant to 50.4-Gy radiation on the rectum and adjacent lymph nodes (Fig. 1). Clinical downstaging was the study primary endpoint and was defined as stage regression 6–8 weeks after neoCRT, using the AJCC 7th edition [29].

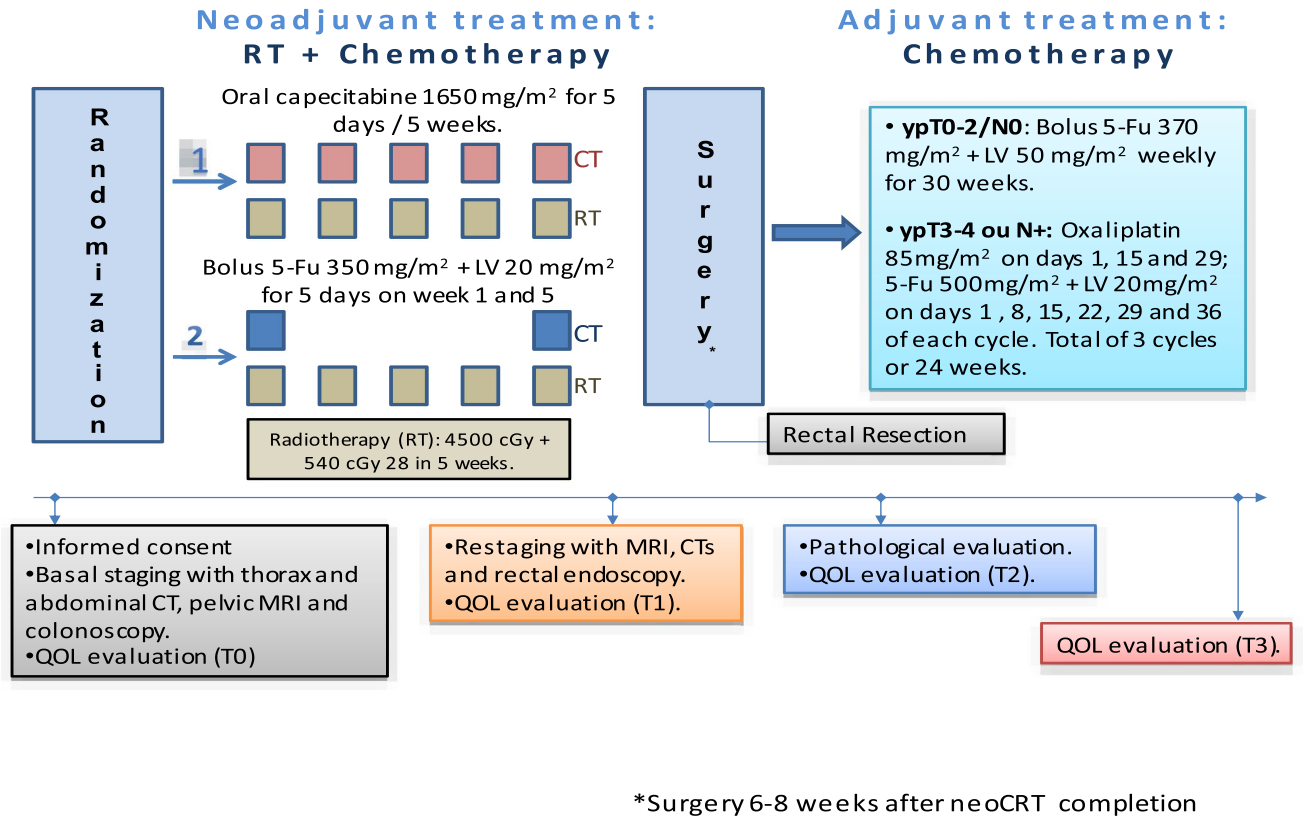


Fig. 1 Study design

Eligibility criteria

All consecutive eligible patients from 18 to 80 years with ECOG performance status 0–1 admitted in this tertiary cancer hospital with rectal adenocarcinoma stages II and III that voluntarily agreed to participate were selected for inclusion. Distance from the anal verge (AV) did not exceed 10 cm measured with rigid proctoscopy. Patients were staged before neoCRT and re-staged 6–8 weeks after it with thorax and abdominal computer tomography (CT), endorectal ultrasonography (EUS), and pelvic magnetic resonance imaging (MRI). Patients were excluded if distant metastasis were found on pre-treatment staging, in case of serious comorbidities, pregnancy, or previous oncological treatments.

Neoadjuvant treatment

Eligible patients were randomized to receive one of the following regimens: oral capecitabine 1650 mg/m^2 in two daily divided doses from Monday to Friday for 5 weeks (group 1) or intravenous bolus 5-Fu (350 mg/m^2) plus leucovorin (20 mg/m^2) days 1 to 5 and 29 to 33 (group 2). Both schemes were concomitant to three-dimensional external beam radiotherapy (50.4 Gy in 28 fractions).

Surgical treatment

Surgical resection consisted of low anterior resection (LAR), intersphincteric resection (ISR), or abdominoperineal resection (APR), according to sphincter invasion

using MRI classification of sphincter invasion after neoCRT [16]. It was planned 6–8 weeks after neoCRT completion. Patients without sphincter complex invasion were submitted to LAR; patients with internal sphincter invasion were candidates to ISR if a > 1-mm circumferential margin was predicted. APR was reserved for patients with external sphincter invasion or intersphincteric plane invasion after neoCRT. Diverting stomas were performed after low colorectal or coloanal anastomosis, and stoma closure was undertaken after completion of the adjuvant chemotherapy.

Adjuvant treatment

Adjuvant chemotherapy was defined by pathological response. Patients with ypT0-2/N0 tumors received bolus 5-Fu 370 mg/m^2 and leucovorin 50 mg/m^2 weekly for 30 consecutive weeks. Patients with ypT3–4 and/or ypN1 tumors received oxaliplatin 85 mg/m^2 on days 1, 15, and 29 of each cycle, and bolus 5-Fu 500 mg/m^2 plus leucovorin 20 mg/m^2 on days 1, 8, 15, 22, 29, and 36 of each cycle. Each of the three cycles consisted of 6 weeks of chemotherapy followed by 2 weeks of rest, totaling 24 weeks. Dose reduction, delay, and discontinuation of treatment have followed the Common Terminology for Adverse Events (CTCAE) version 3.0 guideline.

Follow-up

Patients were followed by medical consultations every 3 months in the first 2 years and every 6 months in the 3 subsequent years until the completion of 5 years of follow-up, disease progression, or death. CT scans and rectal endoscopy were performed every 6 months for detecting recurrences.

Quality of life evaluation

EORTC QLQ C30 [20] and CR38 [21] were applied at five different treatment moments: before neoCRT (T0), 6–8 weeks after neoCRT (T1), 30 days after surgery (T2), after adjuvant chemotherapy (T3), and 1 year after the end of the treatment or stoma closure (T4) (Fig. 2). QLQ-C30 grouped in nine multiple-item scales and six single-item scales and has been tested and validated in the Brazilian population [30]. The multiple-item scales comprise five functional scales (physical, cognitive, emotional, social, and role functioning), and three symptom scales (fatigue, pain, and nausea/vomiting), a global health status/quality-of-life scale, and six single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). All the scales and single-item measures range in score from 0 to 100. A high score for a functional scale and global health status represents a high/healthy level of functioning, but a high score for a symptom scale/item represents a high level of symptomatology/problems. CR38 is a module complementary to C30, comprising 38 questions related to common symptoms and adverse effects of treatment related to

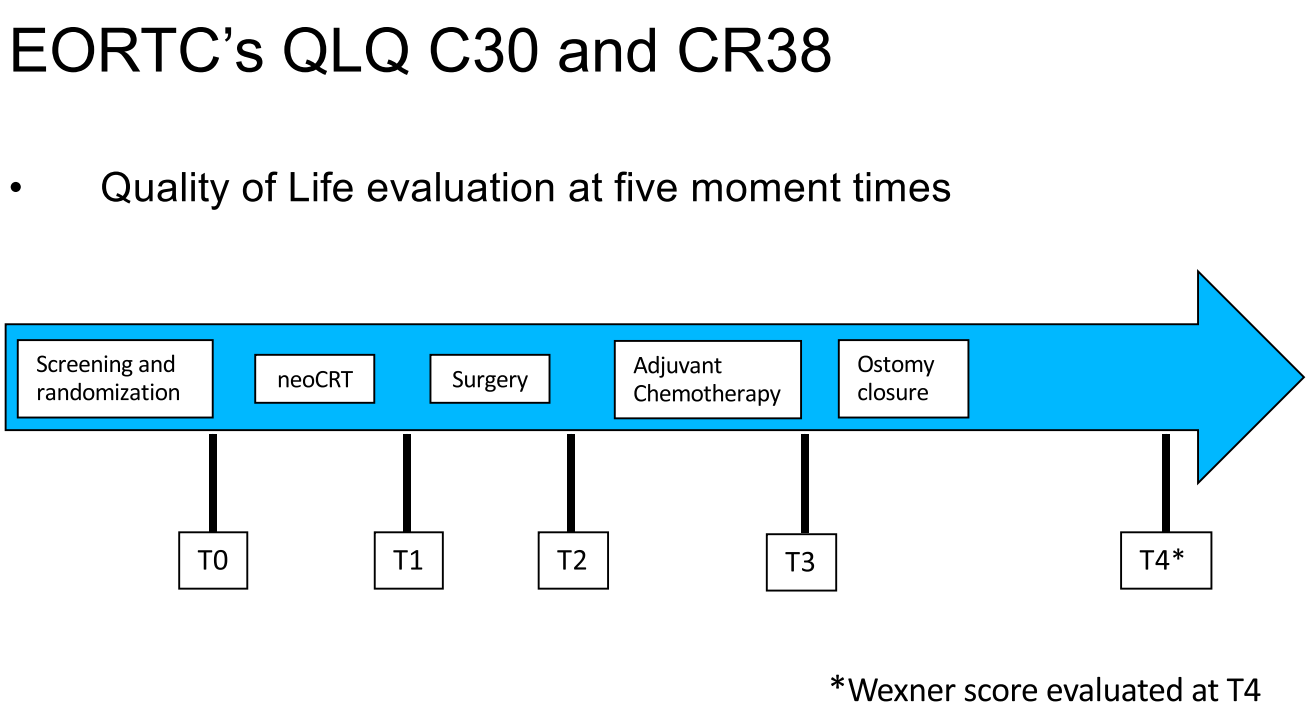


Fig. 2 QOL evaluation times

colorectal cancer and has been validated for Brazilian patients [31]. C30SumScore was calculated as a mean of all the functional and symptom scores excepting Global Health Status and Financial Problems as recommended by the authors, compiling the mean scores of a total of 13 domains. To calculate C30SumScore, the eight symptom scales scores were inverted, a high score meaning few symptoms and better outcomes. To evaluate fecal incontinence after rectal resection and sphincter preservation, we used the Wexner score [32], which comprises 5 questions for fecal incontinence, producing a score from 0 to 20, and it was accessed at T4. The Wexner score is the most widely adopted tool for accessing incontinence in the literature [33] and has been validated for Portuguese [34].

Sample size calculation and randomization

The study was primarily designed to detect difference in clinical downstaging between the two treatment groups assuming 90% of downstaging with capecitabine and 70% with *bolus* 5-Fu/Lv. The estimated sample size was 48 patients in each arm (alpha: 0.05; beta: 80%). Time for accrual was stipulated in 24 months. Randomization was performed in a proportion 1:1 using R software (R *Development Core Team*, 2008) with permuted blocks stratified by tumor distance from AV: > 5 cm or ≤ 5 cm.

Statistical analysis

All statistical analyses were performed using SPSS version 21.0 (SPSS Inc., CA, USA). Continuous variables were displayed as means ± standard deviation (SD) or median with range (minimum and maximum) according to data distribution. Chi-square tests or Fisher exact tests were used to compare categorical variables, Student's *T*-test to compare means of parametrical variables, and the Mann–Whitney *U* test to compare values of non-parametric data. To compare mean QOL scores between treatment arms, the ANCOVA test adjusted for basal clinical data (age, sex, tumor localization, and clinical stage) was used. For comparing longitudinal QOL results, an ANOVA test with Greenhouse–Geisser correction for lack of sphericity was employed combining group 1 and group 2 to increase statistical power. Mean differences of QOL in specific scales were considered clinically relevant if a minimum discrepancy of 10 points was found [35]. For the C30SumScore, a two-tailed *p*-value of less than 0.05 was considered statistically significant [36–38].

Results

Sixty-three patients were randomized between January 2011 and February 2013 (Fig. 3). All patients completed neoCRT with no severe toxicities except form one patient with grade 3 diarrhea and abdominal cramps. One patient refused surgery after a complete clinical response. Two patients quitted the study during follow-up.

Clinical information was available for 61 patients (Table 1). Thirty-one patients were assigned to neoadjuvant capecitabine (group 1) and 30 to 5-Fu/Lv (group 2). Baseline characteristics and treatment results are depicted in Table 1. Groups were similar at baseline, and downstaging, sphincter preservation, surgical access, and Mandard's pathological TRG were comparable after neoCRT. Tumor T stage regression was more frequent in the capecitabine group, and there was a trend for more surgical complications in the 5-Fu/Lv arm.

QOL data from 61 patients were available at T0, 60 at T1, 57 at T2, 51 at T3, and 37 at T4. Reasons for no completion of questionnaires at a given moment were death ($n = 14$), disease progression ($n = 6$), no adherence to follow-up ($n = 3$), and desire to quit the study ($n = 2$). Supplementary Table 1 shows the number of patients available for each scale in five moments. Supplementary Table 2 reports the mean C30 and CR38 scores in all domains including the C30SumScore.

Table 2 shows comparison of QOL scores and the C30SumScore between group 1 and group 2 using covariate adjustment for age, gender, clinical stage, and tumor localization before (T0) and after neoadjuvant treatment (T1). At T0, group 1 patients reported more insomnia (12.3 pts mean difference) but reported less weight loss (− 12.1 pts mean difference). After neoadjuvant treatment, no significant difference in QOL between patients receiving capecitabine or 5-Fu/Lv was shown in any score of C30 questionnaire, but patients in group 1 (capecitabine) reported less micturition problems (15.3 pts mean difference), less gastrointestinal problems (− 15.3 pts mean difference), less defecation problems (11.8 pts mean difference), and more sexual satisfaction (13.3 pts mean difference) in CR38 questionnaire modules. C30SumScore was equivalent before and after neoCRT in the two study groups.

The longitudinal QOL analysis comparing results on five different moments of treatment is depicted in Table 3. Median time intervals between evaluations were T0 to T1 median 14 (11–18) weeks; T1 to T2 median 9 (4–19) weeks; T2 to T3 median 40 (28–95) weeks; and T3 to T4 median 175 (102–227) weeks or 3.3 years. Also, the median time interval from rectal resection to T2 was 5 (4–15) weeks, and to T4 was 214 (148–262) weeks. Role-functioning scores showed improvement after neoCRT (T1) compared to basal evaluation (T0) and worsened after a median time of 5 weeks (range 3–15 weeks) after surgical resection, decreasing 24.4 points at T2 evaluation. Patients also significantly improved at the late evaluation (T4) compared to the postoperative period (T2). Patients also reported more fatigue and appetite loss after surgical resection (an increase of 15.4 and 17.1 points respectively T2 to T1). Constipation improved

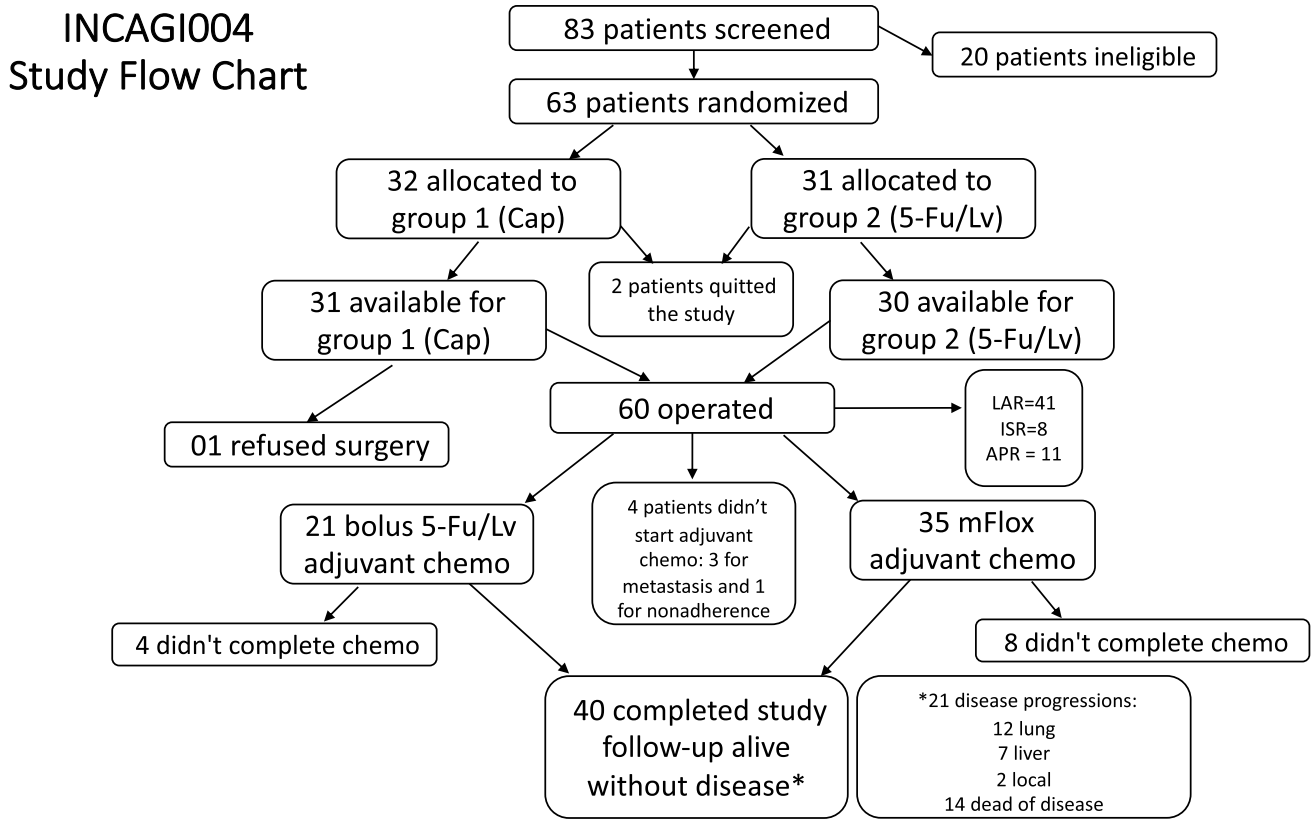


Fig. 3 Study flowchart

after neoCRT (reduction in 11.5 points comparing T0 to T1). Diarrhea was a symptom that worsened at T4 compared to T1 (an increase in 22.2 points), meaning that after stoma closure patients were more symptomatic in this domain than after the chemoradiation period. Both Global Health Status and the new C30SumScore detected improvement in the T1 score compared to T0 (after chemoradiation versus basal scores), but only C30SumScore detected a difference in T2 compared to T1 (postoperative period compared to post-chemoradiation), but this difference did not reach the 10-point range. Interestingly, the Global Health Status score improved at T4 compared to T0 in 15.5 points, a difference that was not identified in any other domain of C30 questionnaire.

Regarding the CR38 modules specific for colorectal cancer, the longitudinal analysis detected improvement in the late evaluation period (T4) compared to the postoperative period (T2) in the following domains: micturition problems (−13.2 pts mean difference), weight loss (−28.7 points mean difference), and sexual functioning (15.5 points mean difference). Comparing the evaluation before treatment (T0) with the available patients at late evaluation at T4, there was a difference at Global Heath Status (15.5 pt mean difference), weight loss (−23.1 pt mean difference), and reduction in defecation problems (−11.0 pt mean difference), but an increase in male sexual problems (47.9 point mean difference). Graphic 1 depicts changes over time that were clinically relevant QLQ-C30 domains, and Graphic 2 shows relevant changes in CR38 domains over time.

Graphic 3 shows temporal changes in QOL using the C30SumScore for each treatment group and for all patients at the five moments of evaluation.

Excluding patients with definitive stoma ($n=8$), patients that had no bowel continuity restored ($n=4$), and patients who had recurrences ($n=16$), 27 patients were evaluated using the Wexner score at T4 with a mean of 9.2 points (SD 4.1). No significant difference in mean incontinence score was found comparing ISR to LAR (10.0 vs 9.1, $p=0.663$). There was no association between level of anastomosis and incontinence when using the Wexner score value of 10 as a cutoff ($p=0.415$). Patients with Wexner score ≥ 10 had more symptoms of diarrhea ($p=0.006$) and defecation problems ($p=0.004$) in QOL scores at T4 (Table 4).

Table 1 Clinical, surgical, and pathological data of patients in both groups of treatment

Patient characteristics	Total $N=61$ (100%)	Group 1 (Cap) $N=31$	Group 2 (5-Fu) $N=30$	p-value
Gender				
Male	33 (54.1)	16 (51.6)	17 (56.7)	0.692*
Female	28 (45.9)	15 (48.4)	13 (43.3)	
Age (mean, SD)	58.5 (11.4)	56.6 (13.4)	60.5 (8.6)	0.182#
BMI (mean, SD)	26.8 (4.6)	25.8 (4.3)	27.7 (4.7)	0,102#
Tumor obstructive	17 (27.8)	9 (29.0)	8 (26.6)	0,845*
Cm from AV (mean)	4,3 (2.7)	4,9 (2.8)	3,7 (2.4)	0,141#
Sphincter invasion (MRI)	13 (21.3)	6 (19.3)	7 (23.3)	0,747*
Basal clinical stage (MRI)				0.129*
I	3	3	0	0.129*
II	23	13	10	
III	35	15	20	
Sphincter preservation	49 (81.6)	25 (83.3)	24 (80.0)	0.111*
Clinical downstaging	37 (61.7)	21 (70.0)	16 (53.3)	0.288*
T stage regression	15 (24.5)	11(35.4)	4(13.3)	**0.042***
pCR	10 (16,6)	7 (23.3)	3 (10.0)	0.165*
Surgical access				0.356*
Videolaparoscopic	30 (50.0)	16 (53.3)	14 (46.6)	0.356*
Laparotomy	18 (30.0)	8 (26.6)	10 (33.3)	
Combined	12 (20.0)	6 (20.0)	6(20.0)	
Surgical complications	12 (20.0)	3 (10.0)	9 (30.0)	0.052*

Cap capecitabine, *5-Fu* 5-fluorouracil, *SD* standard deviation, *BMI* body mass index, *AV* anal verge, *DL* dentate line, *MRI* magnetic resonance imaging, *pCR* pathologic complete response, *CRM* + circumferential resection margin < 1 mm. p-values <0.05 were considered stastiscally significant and are displayed in bold

*Qui-square test

#Student's t-test

Conclusions

- QOL was equivalent between groups after neoCRT except for micturition problems, gastrointestinal problems, defecation problems, and sexual satisfaction favoring the capecitabine arm.
- Overall QOL was improved after neoCRT (T1) but decreased following rectal resection (T2), returning to baseline levels after adjuvant chemotherapy (T3) until the late evaluation (T4).
- Fecal incontinence was high after sphincter preservation (mean 9.2 points using Wexner score) and was equivalent comparing LAR versus ISR.

Discussion

The contemporary treatment for LARC provides long-term survival in most patients, but acute and late sequelae are major setbacks and jeopardize the successfulness of medical interventions. Investigation on new treatment strategies should maintain efforts to improve disease control rates, but optimization of the quality of life after successful treatment becomes a prime directive. Our randomized study was designed to compare clinical response between capecitabine and 5-Fu/Lv combined to radiotherapy in neoadjuvant setting, but also included a dedicated QOL analysis. After neoadjuvant treatment, despite no significant difference in QLQ-C30 scores between patients receiving capecitabine or 5-Fu/Lv, patients in group 1 (capecitabine) reported less micturition problems (15.3 pt mean difference), less gastrointestinal problems (− 15.3 pt mean difference), less defecation problems (11.8 pt mean difference), and more sexual satisfaction (13.3 pt mean difference) in CR38 questionnaire-specific colorectal modules. Coincidently, the clinical response rate (70.0% vs 53.3%) and the pathological complete response rate (23.3.% vs 10.0%) were higher in the capecitabine group, although this was not a statistically significant difference, which might have been explained by the study sample size. Only the T stage regression was higher in the capecitabine group (35.4% vs 13.3%, $p=0.042$). It is possible that this greater tumor downsizing facilitated surgical resection, resulting in less surgical sequelae (less damage to the genitourinary nervous plexus) and less overall surgical complications. The capecitabine group had a tendency to present less complications (Table 1) that was not statistically significant but may have influenced in QOL outcome. There is evidence that surgical complications correlate with worse

Table 2 Mean QOL scores (C30 and CR38) comparing groups 1 and 2 before (T0) and after (T1) neoCRT. Clinically relevant differences are displayed in bold

	T0				T1			
	Group 1 ($n=31$)	Group 2 ($n=30$)	*p*-value	Mean difference	Group 1 ($n=31$)	Group 2 ($n=29$)	*p*-value	Mean difference
EORTC QLQ-C30								
Physical functioning	85.2	88.0	0.577	−2.8	86.4	88.3	0.503	−2.9
Role functioning	80.6	82.0	0.849	−1.4	91.7	89.9	0.720	1.8
Cognitive functioning	77.6	79.4	0.793	−1.8	84.9	87.7	0.598	−2.7
Emotional functioning	66.9	64.6	0.782	2.3	71.8	68.0	0.620	3.8
Social functioning	82.9	77.3	0.449	5.6	86.9	84.2	0.695	2.7
Fatigue	21.7	18.1	0.645	3.6	14.7	11.3	0.434	3.4
Pain	28.1	26.5	0.821	1.6	19.6	11.6	0.256	7.9
Dyspnea	10.0	4.0	0.386	6.0	9.1	3.8	0.291	5.3
Insomnia	29.0	16.7	0.244	**12.3**	15.6	18.5	0.714	−2.9
Appetite Loss	21.9	12.6	0.144	9.3	10.9	3.3	0.213	7.5
Nausea	2.1	5.8	0.258	−3.7	0.0	0.0	-	0
Constipation	33.6	25.4	0.477	8.2	11.0	16.5	0.517	5.4
Diarrhea	24.0	17.3	0.475	6.6	4.1	7.7	0.361	−3.5
Financial difficulties	31.8	37.2	0.612	5.4	21.1	27.3	0.514	−6.2
Global health status	71.6	64.2	0.200	7.4	77.5	76.4	0.851	1.0
C30SumScale	78.8	81.8	0.450	−3.0	87.4	88.2	0.788	−0.8
EORTC CR38								
Micturition problems	30.8	38.8	0.373	−5.0	30.7	46.1	0.525	**−15.3**
Gastrointestinal problems	24.0	20.4	0.518	3.6	7.6	22.8	0.096	**−15.3**
Weight Loss	24.8	36.9	0.267	**−12.1**	12.7	21.3	0.274	−8.6
Chemotherapy side effects	16.7	9.7	0.240	7.0	15.5	11.1	0.219	4.3
Defecation problems	34.1	35.9	0.736	−1.7	15.5	23.3	0.168	**−11.8**
Male sexual problems*	-	-	-	-	-	-	-	-
Female sexual problems*	-	-	-	-	-	-	-	-
Stoma related problems*	-	-	-	-	-	-	-	-
Body image	8.8	10.7	0.742	−1.9	4.6	2.9	0.611	2.3
Future perspectives	55.5	63.3	0.726	−7.9	57.4	59.2	0.921	−1.8
Sexual functioning	48.5	46.8	0.883	1.6	62.5	60.5	0.848	2.0
Sexual satisfaction	55.3	58.5	0.827	−3.2	71.2	57.9	0.333	**13.3**

Using ANCOVA multivariate analysis adjusted for age, gender, tumor height, and clinical stage

QOL quality of life, *neoCRT* neoadjuvant chemoradiotherapy

*Insufficient number of valid responses

Table 3 Longitudinal comparison of QOL scores using ANOVA's repeated measure test and Greenhouse-Geiser correction for lack of sphericity

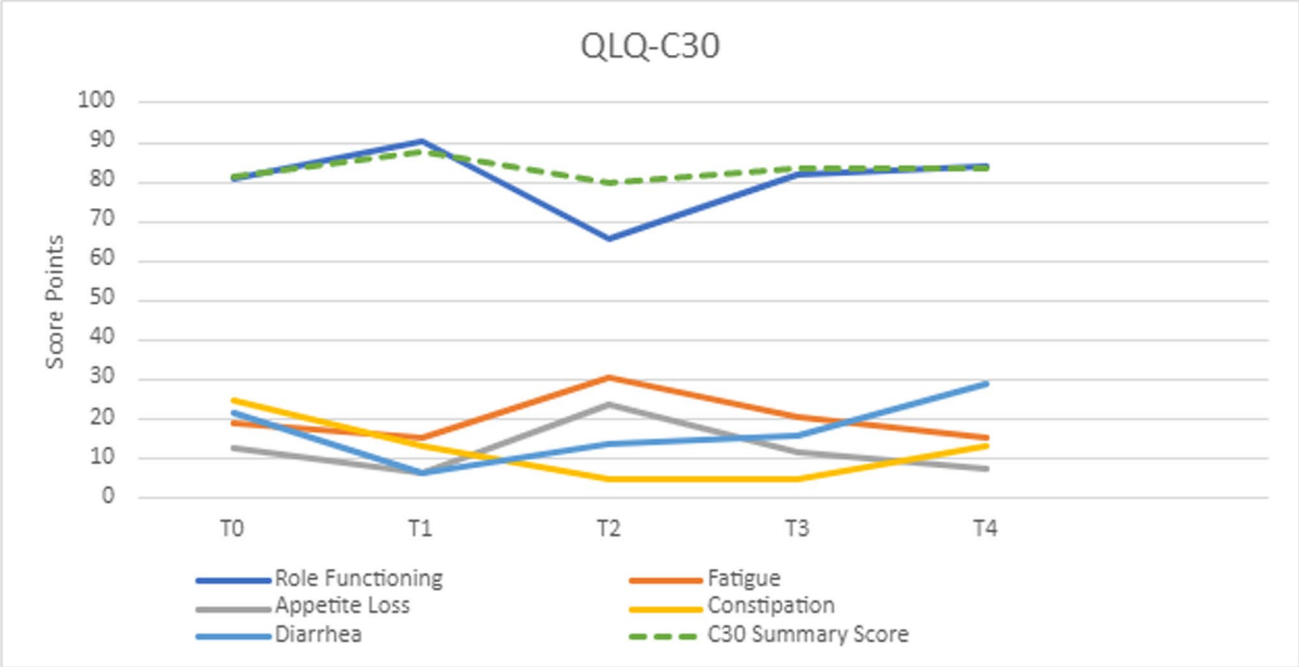
EORTC QLQ-C30	T0	T1	T2	T3	T4	Sphericity	ANOVA (G.Geisser)	Difference
Physical functioning	87.9	85.2	78.4	81.0	86.7	0.353	$F(3.47–125.01)=2.60$; $p=0.047$	No
Role functioning	81.0	90.1	65.7	82.0	83.8	0.000	$F(3.00–108.18)=5.93$; $p=0.001$	T0 < T1; T1 > T2; T2 < T4
Cognitive functioning	79.3	86.9	81.1	81.1	77.4	0.540	$F(3.61–129.91)=1.64$; $p=0.174$	No
Emotional functioning	64.2	73.0	67.8	68.0	70.7	0.007	$F(3.05–109.82)=1.17$; $p=0.322$	No
Social functioning	73.8	87.7	73.2	80.3	77.2	0.484	$F(3.64–134.65)=2.29$; $p=0.069$	No
Fatigue	18.7	15.1	30.5	20.7	15.4	0.305	$F(3.43–119.96)=5.28$; $p=0.001$	T2 > T1
Pain	27.0	19.4	23.4	21.2	16.7	0.881	$F(3.77–135.62)=1.23$; $p=0.298$	No
Dyspnea	4.6	3.7	1.8	3.7	4.6	0.002	$F(2.92–102.3)=0.307$; $p=0.815$	No
Insomnia	19.8	21.6	30.6	26.1	21.6	0.010	$F(3.11–112.08)=1.05$; $p=0.375$	No
Appetite loss	12.6	6.3	23.4	11.7	7.2	0.001	$F(2.90–104.673)=3.94$; $p=0.011$	T2 > T1
Nausea	4.1	0.0	3.2	5.0	2.7	0.000	$F(2.27–81.89)=2.15$; $p=0.116$	No
Constipation	24.8	13.3	4.7	4.7	13.3	0.000	$F(2.86–97.40)=4.69$; $p=0.005$	T0 > T2; T0 > T3
Diarrhea	21.3	6.5	13.9	15.7	28.7	0.035	$F(3.26–114.06)=3.34$; $p=0.019$	T4 > T1
Financial difficulties	35.1	24.3	33.3	25.2	26.1	0.384	$F(3.51–126.23)=1.40$; $p=0.243$	No
Global health status	64.7	74.3	71.6	75.2	80.2	0.364	$F(3.53–127.07)=4.37$; $p=0.004$	T0 < T1; T0 < T4
C30SumScale	81.3	87.4	79.6	83.5	83.4	0.001	$F(3.08–110.99)=3.195$; $p=0.025$	T0 < T1; T1 > T2;
EORTC CR38	**T0**	**T1**	**T2**	**T3**	**T4**		***p* value**	
Micturition problems	38.1	41.4	45.6	39.0	32.4	0.089	$F(3.43–123.65)=2.83$; $p=0.035$	T2 > T4
Gastrointestinal problems	21.1	15.7	16.9	16.9	19.1	0.440	$F(3.56–128.26)=1.07$; $p=0.368$	No
Weight loss	34.2	16.7	39.8	16.7	11.1	0.640	$F(3.62–126.73)=8.05$; $p=0.001$	T0 > T4; T1 < T2; T2 > T3; T2 > T4
Chemotherapy side effects	10.2	12.6	16.1	14.4	17.4	0.090	$F(3.17–114.431)=1.65$; $p=0.179$	No
Defecation problems	30.1	15.3	-	-	19.1	0.318	$F(1.76–29.99)=6.93$; $p=0.004$	T0 > T1; T0 > T4
Male sexual problems	0.0	27.1	52.1	50.0	47.9	0.090	$F(2.47–17.28)=3.74$; $p=0.037$	T0 < T4
Female sexual problems	-	-	-	-	-	-	–	N.A
Stoma-related problems	-	-	31.1	35.5	36.8	0.689	$F(1.85–18.53)=0.39$; $p=0.668$	No
Body image	14.1	12.9	34.4	38.1	24.9	0.028	$F(3.27–117–84)=9.60$; $p<0.001$	T0 < T2; T0 < T3; T1 < T2; T1 < T3
Future perspectives	68.5	59.3	61.1	49.1	50.9	0.001	$F(2.8–98.3)=1.71$; $p=0.171$	No
Sexual functioning	37.7	36.7	15.6	28.3	31.1	0.000	$F(2.45–71.11)=4.76$; $p=0.007$	T0 > T2; T1 > T2; T3 > T2;T4 > T2
Sexual satisfaction	70.0	63.3	-	-	-	-	$F(1.00–19.00)=1.65$; $p=0.214$	No

N.A. not applicable due to insufficient number of patient answers

functional outcomes [39] and exert a negative and lasting effect on quality of life [40]. In the CLASSIC randomized trial comparing open versus laparoscopic resection for colorectal cancer, 35% of patients experienced at least one postoperative complication, and those patients presented worse QOL scores at the 36-month follow-up on Physical Functioning, Role Functioning, Social Functioning, and Body Image [41]. These results suggest that surgical outcomes rather than treatment regimen may justify the differences in specific quality-of-life domains.

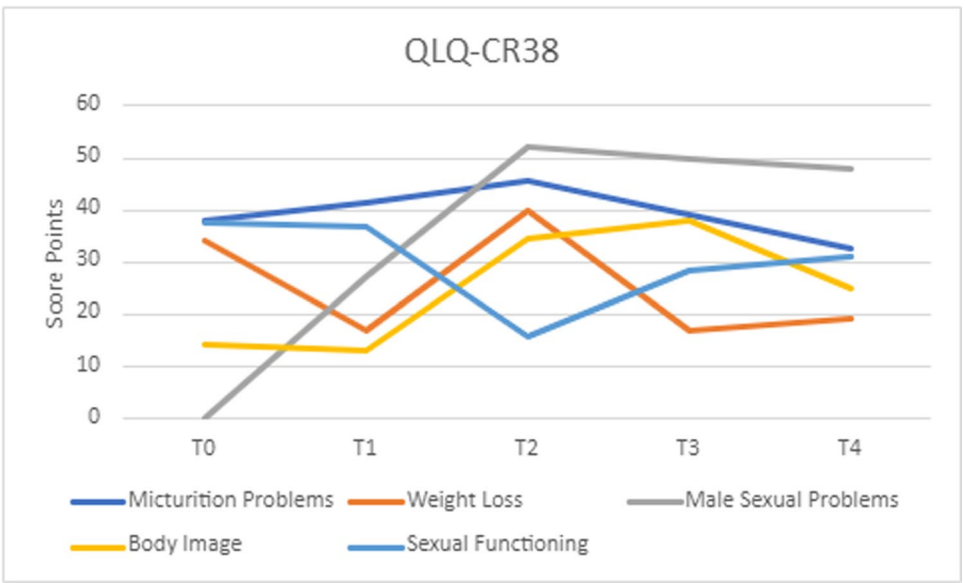
No previous publications compared QOL after these two drug regimens in the neoadjuvant setting, but some reports compared these two drugs in adjuvant or palliative settings. A nonrandomized Taiwanese study published in 2015 evaluated 123 elderly stage III patients after adjuvant CT compared QOL and treatment costs of capecitabine vs 5-Fu/Lv, associated or not with oxaliplatin [42]. After adjusting confounding variables and baseline characteristics, QOL using capecitabine was not inferior to 5-Fu/Lv and reduced costs. Similarly, two previous studies compared palliative treatment in metastatic colorectal cancer using capecitabine and 5-Fu/Lv in combination with oxaliplatin showed no difference in QOL between treatment groups [43, 44]. Nevertheless, comparing the moments before and after neoCRT we balanced the effect of surgical resection and excluded the interference of oxaliplatin, which allowed a direct comparison of the two drugs in combination to radiotherapy.

The second question to be answered was regarding the functional results after sphincter preservation, which was an important endpoint in our study. Combining accurate preoperative imaging (MRI and EUS) with modern surgical techniques, the sphincter preservation rate was 81.6% in our study, considering all patients. We have accomplished to reestablish the intestinal continuity using coloanal anastomosis and/or intersphincteric resection after good clinical responders even with low rectal cancers close to sphincter



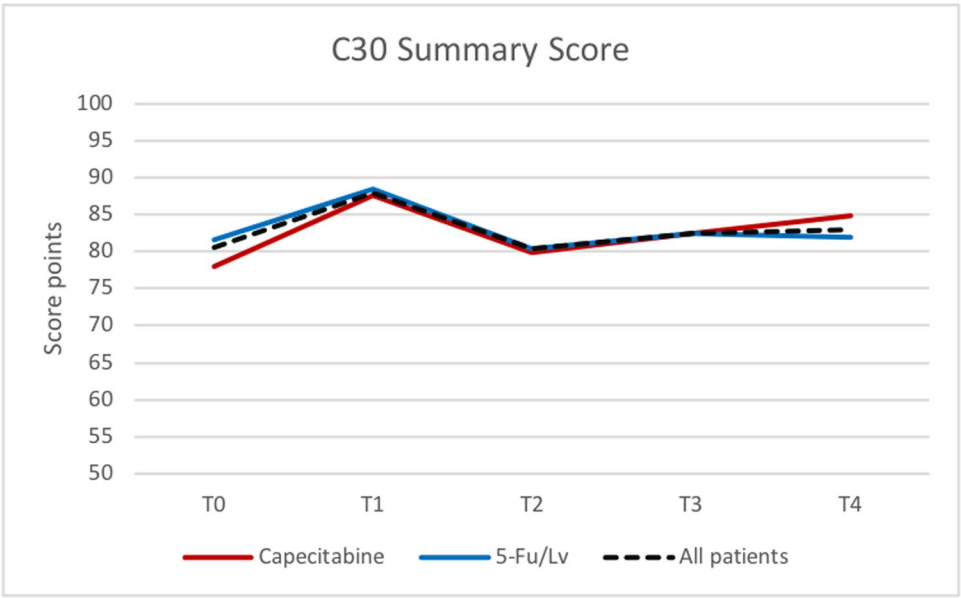
Graphic 1 Changes over time that were clinically relevant on individual QLQ-C30 domains and C30SumScore combining groups 1 and 2. A high score for a functional scale (Role Functioning) and global represents a high/healthy level of functioning, but a high score for a symptom scale (Appetite Loss, Diarrhea, Fatigue and Constipation) represents a high level of symptomatology/problems

Graphic 2 Changes over time that were clinically relevant on individual CR38 scales over time combining groups 1 and 2 using the same methodology



complex, although our functional results were often suboptimal (mean Wexner score of 9.2). Interestingly, no functional difference was observed after ISR compared to LAR.

Both neoadjuvant schemes were effective in ameliorating general cancer symptoms and health status after neoCRT (T1) compared with baseline (T0), expressed as improvements in role functioning, global health status, and C30SumScore scales of QLQ C30, reduction in defecation problems of CR38 questionnaire, and no worsening of any domain of both questionnaires. In contrast, the adverse effects of rectal resection in QOL were evident: four of the C30 scales and three of the CR38 scales had worse scores comparing T1 to T2. Not surprisingly, patients had nonsignificant improvement in QOL 6 months after rectal resection, except for weight loss and sexual functioning despite receiving many cycles of adjuvant chemotherapy from T2 to T3. This time



Graphic 3 Temporal changes in QOL using the C30SumScore for each treatment group and for all patients at the five moments of evaluation.

Table 4 Mean QOL scores comparing patients with Wexner score < 10 vs ≥ 10. Statistically significant *p*-values are displayed in bold

	Wexner < 10	Wexner ≥ 10	Mean Difference	p-value
EORTC QLQ-C30				
Physical functioning	88.2	87.6	0.6	0.930
Role functioning	91.0	79.8	11.3	0.250
Cognitive functioning	85.9	71.4	14.5	0.140
Emotional functioning	75.0	65.5	9.5	0.354
Social functioning	89.8	73.8	15.9	0.140
Fatigue	11.1	19.8	−8.7	0.202
Pain	19.2	20.2	−1.0	0.935
Dyspnea	5.1	7.1	−2.0	0.754
Insomnia	15.4	11.9	3.5	0.677
Appetite loss	2.6	5.1	−2.6	0.558
Nausea	1.3	4.8	−3.5	0.395
Constipation	15.4	14.3	1.1	0.906
Diarrhea	15.4	52.4	−37.0	**0.006**
Financial difficulties	25.6	28.6	−2.9	0.851
Global health status	84.6	70.8	13.8	0.077
C30SumScale	88.0	80.1	8.0	0.201
EORTC CR38				
Micturition problems	25.6	38.9	−13.3	0.080
Gastrointestinal problems	15.9	27.1	−11.3	0.109
Weight loss	2.6	15.4	−12.8	0.105
Chemotherapy side effects	11.1	21.4	−10.3	0.187
Defecation problems	14.7	31.5	−16.9	**0.004**
Male sexual problems	46.7	50.0	−3.3	0.868
Female sexual problems	38.9	50.0	−11.1	0.874
Stoma-related problems	NA	NA	NA	NA
Body image	22.2	25.4	−3.2	0.779
Future perspectives	50.0	59.5	−9.5	0.556
Sexual functioning	18.0	32.2	−14.2	0.179
Sexual satisfaction	33.3	46.7	−13.3	0.524

interval may have allowed improvement in patients' perception of surgical morbidity. Although our sphincter preservation rate was over 80%, patients had to deal with temporary stomas for at least 6 months.

Minimally invasive surgery for colorectal cancer offers advantages such as better cosmesis, shorter hospitalization period, decreased postoperative pain, and earlier return to work. In our study, 70% of patients had laparoscopic or combined approach (laparoscopy for left colon mobilization and open for TME), with no significant difference between groups. In the large randomized COLOR II trial with 1044 patients, no significant difference in local recurrence and survival was found comparing open and laparoscopic approach [45]. In the aforementioned study using the EORTC CR38 questionnaire, all aspects of sexual dysfunction and micturition symptoms deteriorated by 4 weeks after surgery, and interestingly no difference in genitourinary and sexual disfunction comparing open and laparoscopic group was detected at any point.

Finally, we included a late fecal continence evaluation 1 year after stoma reversal using the Wexner score, which has been recently translated and validated in Portuguese [34]. We found an average high score of fecal incontinence that did not correlate to anastomosis level but correlated to QOL scores of diarrhea and defecation problems.

Our participants have never recovered from some sequelae of the treatment even at late evaluation after a median time interval of 49 months. Compared to basal evaluation (T0), patients improved from general cancer symptoms (Global Health Status) and ameliorated on weight loss and constipation, but developed male sexual disfunction. Comparing the late evaluation (T4) with the postoperative period (T2), patients had improvement in role functioning, weight loss, micturition problems, and sexual functioning, which may reflect that some autonomic sequalae can ameliorate with time, but also can reflect a tendency of patients to change the perception of the same condition over time, for example if their cancer is controlled, a phenomenon called "response shift" [46, 47]. The literature supports our findings of symptom improvement over time. A study from the Netherlands identified worse C30SumScore, physical functioning, fatigue, and dyspnea in patients who received adjuvant chemotherapy compared to observation, but this difference disappeared 12 months after surgery [48]. Other studies demonstrate stabilization of LARS 1 year after surgery [49] and that patients after a long-time follow-up still present significant disfunction [50].

Concerning the specific colorectal cancer module, CR38 was commonly used in adjunct to QLQ-C30 to measure specific domains of quality of life in colorectal cancer patients, but criticism has emerged because questions concerning sexuality are often unanswered on CR38; these questions were suppressed or revised in the CR29 version [22]. CR29 emerged later and was in validation when we started our study. Indeed, in our study, few patients answered questions about sexual problems (only four were available to compare T0 and T1) and sexual satisfaction (only 19 of 61 were available).

Our study was the first to use the C30SumScore to compare results of QOL over time in five moments beginning at pretreatment levels, and it detected significant differences in QOL after neoCRT and rectal resection. After neoCRT, patients reported an increase in 6.1 points in C30SumScore. After rectal resection, patients reported a decrease in 7.8 points in mean scores. The C30SumScore appears to add relevant information to clinical practice allowing a comparison between treatment groups and detecting relevant temporal changes in QOL. It was designed to measure QOL changes over time and provide a more robust and reliable measure of overall QOL than the Global Health Status scale and has been used to access the impact of clinical interventions on QOL [48, 51]. It has also been demonstrated to correlate with prognosis [51, 52].

Unfortunately, our study leaves unanswered an old dilemma concerning better selection of patients for sphincter preservation after low rectal cancer resection. We did not detect differences in Wexner scores comparing patients with LAR to ISR, and both groups showed moderate to high levels of incontinence (mean 9.1 versus 10.0 points, respectively). A meta-analysis published in 2015 including 13 studies from 2001 to 2015 comprised data from 1805 patients using QLQ-C30 and CR38 [23]. Their main objective was to compare QOL in patients submitted to LAR vs APR, and QOL questionnaires were applied after 12 months of surgery. Patients with sphincter preservation had better social functioning and better body image, but more symptoms of constipation. One study from Spain evaluated QOL compared to APR versus LAR in 84 patients after neoCRT and surgery [53]. After a mean follow-up of 48.7 months, no significant difference in QLQ-C30 scores was detected. Using the CR29 questionnaire, only the stool frequency score was increased in LAR patients (33.3 vs 14.3 points). Another study compared QOL and functional results using the Wexner score in 14 patients submitted to ISR versus 22 patients submitted to APR and perineal colostomy [54]. ISR patients had worse Physical Functioning (84.1 vs 100.0 points) but less Defecation Problems compared to perineal colostomy (57.1 vs 90.5 points). The Wexner score was similar between two groups (median 11 in ISF versus 10 in APR), which was comparable to our results of ISR (median Wexner score of 10). A matched group analysis from Heidelberg, Germany, compared QOL results of LAR, ISR, and APR in 131 patients from a prospective database [55]. They found that physical functioning scores were better after LAR and ISR compared to APR (82.2 and 80.2 vs 69.9 points), but constipation and diarrhea were both more frequent in

LAR and ISR compared to APR. ISR had a mean higher Wexner score compared to LAR (12.9 vs 9.5), a difference that was not significant in our series. A previous study from Illinois, USA, also found better physical functioning scores after sphincter preservation in a retrospective study (94 vs 87 points), but also more constipation (16 vs 8 points) and decreased sexual functioning (27 vs 76 points) [56]. These suboptimal functional results after curative resection of low rectal cancer motivates investigation of less aggressive approaches to good clinical responders, including the non-operative management that has been explored in recent literature, including our own institution's experience [57, 58].

New strategies are under investigation to decrease toxicity and QOL impairment. Avoiding radiotherapy would probably reduce a degree of pelvic toxicity ameliorating anorectal function after rectal resection, and some studies demonstrated promising response rates using isolated neoadjuvant chemotherapy [59, 60]. Our group has recently adopted the total neoadjuvant treatment, in which all cycles of systemic chemotherapy are delivered before rectal resection with the addition of short-course radiotherapy (SHORT-ICAR Trial, ClinicalTrials.gov Identifier: NCT04674696). This strategy is aimed to improve response, increase compliance rates, and prevent distant relapse, allowing stoma reversal 1 month after TME and the possibility of organ preservation after clinical complete response.

Finally, our study was limited due to incomplete accrual, which may have limited the statistical power to detect small outcome differences between the two treatment arms, as only 63 of 96 patients were randomized after 2 years because some stage I and many stage IV patients were later excluded after ultimate radiological review. Nevertheless, we were able to show a significant difference in QOL in different phases of treatment combining the two treatment arms. We also did not include manometric evaluation, which would give additional information regarding the suitable candidates to sphincter preservation in low rectal cancer cases. Despite this possible caveat, manometry is not widely available as it depends on dedicated equipment and expertise, and many QOL of studies after rectal cancer treatment do not report manometry data. Most studies, including ours, focus on patient-reported outcomes, as the Wexner scale and EORTC questionnaires, which make our results comparable to literature and applicable into clinical practice. One last limitation was that the individual scales of female sexual problems and sexual satisfaction had insufficient responses to allow some of the analysis.

Abbreviations 5-Fu/Lv: 5-Fluorouracil and leucovorin; AJCC: American Joint Commission on Cancer; APR: Abdominoperineal resection; AV: Anal verge; C30SumScore: C30 Summary Score; CT: Computer tomography; CTCAE: Common Terminology for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; EUS: Endorectal ultrasound; INCA: *Instituto Nacional de Cancer* (National Cancer Institute of Brazil); ISR: Intersphincteric resection; LAR: Low anterior resection; LARC: Locally advanced rectal cancer; LARS: Low anterior resection syndrome; MRI: Magnetic resonance imaging; neoCRT: Neoadjuvant chemoradiotherapy; QLQ-C30: Quality of Life Questionnaire C30; QOL: Quality of life; SD: Standard deviation; TME: Total mesorectal excision; USA: United States of America

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Author contribution All the authors made substantial contributions to the manuscript as follows:

Study concepts: Carlos Gil Ferreira and Eduardo Linhares. Study design: Fernando Meton Vieira, Rodrigo Otavio de Castro Araujo, Ana Paula Ornellas. Data acquisition: Rodrigo Otavio de Castro Araujo, Simone Guaraldi and Claudia Carrada. Quality control of data and algorithms: Ana Paula Ornellas, Ivanir Martins, Claudia Carrada. Data analysis and interpretation: Rodrigo Otavio de Castro Araujo e Luiz Claudio Santos Thuler. Statistical analysis: Rodrigo Otavio de Castro Araujo e Luiz Claudio Santos Thuler. Manuscript preparation: Rodrigo Otavio de Castro Araujo. Manuscript editing: Marcus Vinicius Valadão and Simone Guaraldi. Manuscript review: all the authors above.

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Data availability The datasets during and/or analyzed during the current study are publicly available at Mendeley dataset as: Araujo, Rodrigo Otavio (2021), "INCAGI004", Mendeley Data, V1, https://doi.org/10.17632/75vdm7phv9.1. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate This was a prospective study approved by the Ethics Committee of National Cancer Institute of Brazil (INCA) in 2010 under register number 83/10 (NCT03428529). All patients voluntarily agreed to participate after informed consent.

Consent for publication All authors declare that they consented to submit the paper.

Competing interests The authors declare no competing interests.

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