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 QOL in a randomized trial comparing two neoadjuvant regimens for locally advanced rectal cancer.

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 one year after end of treatment or stoma closure (T4). Wexner scale was used for continence evaluation at T4. A C30SummaryScore (Geisinger et cols) was calculated to compare QOL results.

Results: 32 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). pCR was 23.3% in group 1 and 10.0% in Group 2(p=0.165). Sphincter preservation was 83.3% in Group 1 and 80.0% in Group 2(p=0.111). No difference in QOL was detected comparing the two treatment groups before and after neoCRT. C30SummaryScore detected improvement comparing T0 to T1 and deterioration comparing T1 to T2 (p=0.025), and global health status improved at T1 and T4 compared to T0(p=0.004). Mean Wexner scale score was 9.2, and a high score correlated with symptoms of diarrhea and defecation problems at T4.

Conclusions: Clinical and pathological response rates were equivalent in both treatment groups. QOL was improved after neoCRT corresponding to clinical response but decreased following rectal resection. Wexner score was high after sphincter preservation. C30SummaryScore was a useful tool to detect differences in overall QOL in EORTCs multiple item questionnaire.

Trial registration: *NCT03428529. Registered 02/09/2018 - Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT03428529.*

Background

Colorectal cancer is the third most common malignant neoplasia worldwide (1.4 million new cases/year)(1). In Brazil is the third most frequent cancer in men and second in woman(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 stage II and III)(3). Neoadjuvant chemo radiotherapy (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) and phase 3 trials showing comparable efficacy(5, 8, 9). It 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 to the neoadjuvant treatment has resulted in 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 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), and 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 whilst other may get worse. For example, some studies favor sphincter preservation (23) while others suggest equivalent or worse results comparing patients with low rectal anastomosis to 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 Global QOL scale could not detect deteriorating QOL in patients with progressive and terminal disease (25).

In 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 financial problems scale and global QOL scale. This so denominated C30SumScore has been tested in a non-small cell Lung cancer study including 326 patients three months after lung resection and demonstrated better sensitivity to detect postoperative changes compared to the global QOL score(27). In addition, the C30SumScore was demonstrated to perform better than the global QOL scale and the physical functioning scale in 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 and the new summary score to detect differences associated to the clinical response and to the surgical therapy in a randomized prospective trial comparing two different neoCRT regimens in a Brazilian cancer reference hospital.

Objective

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 Ethics Committee of National Cancer Institute of Brazil (INCA) in 2010 under register 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. Figure 1 illustrates the study design. Clinical downstaging was the study primary endpoint and was defined as stage regression 6-8 weeks after neoCRT, using AJCC 7th edition(29).

Eligibility criteria

All eligible consecutive patients from 18 to 80 years with ECOG performance status 0-1 admitted in this single tertiary cancer hospital with rectal adenocarcinoma stage II and III that voluntarily agreed to participate were selected for inclusion. Distance from anal verge (AV) should 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 treatment.

Neoadjuvant treatment

Eligible patients were randomized to receive one of the following regimens: oral capecitabine 1650mg/m^2 in two daily divided doses from Monday to Friday for five weeks (Group 1) intravenous bolus 5-Fu (350mg/m^2) plus Leucovorin (20 mg/m^2) days 1 to 5 and 29 to 33 (Group 2). Both schemes were concomitant to external bean three-dimension 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) and 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 >1mm was predicted; and 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 the adjuvant chemotherapy completion.

Adjuvant treatment

Adjuvant chemotherapy was defined by pathological response. Patients with ypT0-2/N0 tumors received bolus 5-Fu 370mg/m^2 and Leucovorin 50mg/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 cycle consisted of 6 weeks of chemotherapy followed by 2 weeks of rest, totaling 3 cycles, for a total of 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 three months in the first two years and every six months in the three subsequent years until the completion of five 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 one year after the end of the treatment or stoma closure (T4) (Figure 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 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. Wexner score (32), that has been validated for Portuguese(33) comprises 5 questions for fecal incontinence, producing a score from 0 to 20 and it was accessed at T4.

Sample size calculation and randomization

The study was primarily designed to compare 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 analysis was performed using SPSS version 21.0 (SPSS Inc., California, 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 covariance test adjusted for basal clinical data (age, sex, tumor localization and clinical stage) was used. For comparing longitudinal QOL results ANOVA test with Greenhouse-Geisser correction for lack of sphericity was employed. Mean differences of QOL were considered clinically significant if a minimum discrepancy of 10 points was found.

Results

63 patients were randomized between January 2011 and February 2013. 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. 31 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 clinical response (downstaging, sphincter preservation and Mandard tumor regression grade) was comparable after neoCRT (Table 1). 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 5 moments. Figure 3 illustrate the study flow chart. Supplementary Table 2 reports the mean C30 and CR38 scores in all domains including the C30SumScore.

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

Patients Characteristics	Total N=61	Group 1(Cap) N=31	Group 2(5-Fu) N=30	p-value
Gender	33 (54.1)	16 (51.6)	17 (56.7)	0.692*
Male	28 (45.9)	15 (48.4)	13 (43.3)	
Female				
Ethnicity	47 (77.0)	22 (71.0)	25 (83.3)	0.337*
White	6 (9.8)	3 (9.7)	3 (10.0)	
Black	8 (13.1)	6 (19.4)	2 (6.7)	
Mixed				
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 ≤50 mm AV	30 (49.2)	14 (41.1)	16 (53.3)	0.523*
Tumor ≤10 mm DL	14 (22.9)	4 (12.9)	10 (33.3)	0.111*
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)	3	3	0	0.129*
I	23	13	10	
II	35	15	20	
III				
Sphincter preservation	49 (81.6)	25 (83.3)	24 (80.0)	0.111*
Sphincter preservation (tumors ≤5cm from AV)	20(66.6)	9(64.2)	11(68.7)	0.550*
Clinical Downstaging	37 (61.7)	21 (70.0)	16 (53.3)	0.288*
pCR	10 (16.6)	7 (23.3)	3 (10.0)	0.165*
Mandard 1-2	21 (35.0)	13 (43,3)	8 (26.6)	0.175*

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 <1mm. * Qui-square test #Student´s t-test.

Patients Characteristics	Total N=61	Group 1(Cap) N=31	Group 2(5-Fu) N=30	p-value
CRM +	9(15.0)	6(20.0)	3(10.0)	0.472*

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 <1mm. * Qui-square test #Student´s t-test.

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 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 miccional 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.

Table 2: Mean QOL scores (C30 and CR38) comparing Group 1 and 2 before (T0) and after (T1) neoCRT

EORTC QLQ-C30	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
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	**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**
Miccional 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

QOL: Quality of Life; neoCRT: neoadjuvant chemoradiotherapy; using ANCOVA multivariate analysis adjusted for age, gender, tumor height and clinical stage. *: insufficient number of valid responses

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; T3 to T4 median 175(102-227) weeks or 3.3 years. Also, the median time interval from rectal resection to T2 was five (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 five 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 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 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 T1 score compared to T0 (after chemoradiation versus basal scores), but only the C30SumScore detected difference in T2 compared to T1 (postoperative period compared to post chemoradiation), but this difference did not reach the 10-points range. Interestingly, 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.

Table 3
Longitudinal comparison of QOL scores using ANOVA's repeated measures 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

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

EORTC QLQ-C30	T0	T1	T2	T3	T4	Sphericity	Anova (G.Geisser)	Difference
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**	
Miccional 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

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

EORTC QLQ-C30	T0	T1	T2	T3	T4	Sphericity	Anova (G.Geisser)	Difference
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.								

Regarding the CR38 modules specific for colorectal cancer, the longitudinal analysis detected improvement in the late evaluation period (T4) compared to postoperative period (T2) in the following domains: miccional 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 pts mean difference); weigh loss (-23.1 pts mean difference), reduction in defecation problems (-11.0 pts mean difference) but an increase in male sexual problems (47.9 points mean difference).

Graphic 1 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 Wexner score at T4 with a mean of 9.2 points (SD 4.1). No difference in mean incontinence score was found comparing ISR to LAR (10.0 vs 9.1, p=0.663)., There were no association between level of anastomosis and incontinence assuming the Wexner score value of 10 as 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 4
Mean QOL scores comparing patients with Wexner Score <10 vs ≥10. Statistically significant values were displayed in bold.

EORTC QLQ-C30	**Wexner<10**	**Wexner≥10**	**Mean Difference**	**p-value**
Physical functioning	88.2	87.6	0.6	0.930
Role functioning	91.0	79.8	11.3	0.250
Cognitive funcioning	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	**Wexner<10**	**Wexner≥10**	**Mean Difference**	**p-value**
Miccional 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

EORTC QLQ-C30	Wexner<10	Wexner≥10	Mean Difference	p-value
Sexual functioning	18.0	32.2	-14.2	0.179
Sexual satisfaction	33.3	46.7	-13.3	0.524

Conclusions

- The two neoCRT regimens using either oral capecitabine or intravenous bolus 5-Fu/Lv combined to radiotherapy achieved comparable clinical and pathological response rates.
- QOL was equivalent between groups after neoCRT except for miccional problems, gastrointestinal problems, defecation problems and sexual satisfaction favoring the capecitabine arm.
- QOL was improved after neoCRT but decreased following rectal resection.
- Wexner score was high after sphincter preservation (mean 9.2 points) and was equivalent comparing LAR versus ISR.
- C30SummaryScore was a useful tool to detect statistical differences in overall QOL comparing different phases of protocol treatment.

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. In consonance, 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. In the present study we assumed that EORTC's QOL scores would reflect clinical differences in disease responses according to treatment group results. After neoadjuvant treatment, despite no difference in QLQ-C30 scores between patients receiving capecitabine or 5-Fu/Lv was found, patients in group 1 (capecitabine) reported less miccional 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 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 not statistically which might have been explained by the sample size enrolled in the study. No previous publications compared QOL after these two drug regimens in 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 to oxaliplatin(34). After adjusting confounding variables and baseline characteristics, QOL using capecitabine was not inferior to 5-Fu/Lv and reduced costs. In accordance, two previous studies compared palliative treatment in metastatic colorectal cancer using capecitabine and 5-Fu/Lv in combination to oxaliplatin showed no difference in QOL between treatment groups(35, 36). 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) to 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 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 to baseline (T0), expressed as improvements in role functioning, global health status and C30SumScore scales of QLQ C30 and 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 six months after rectal resection, except for weight loss and sexual functioning despite receiving many cycles of adjuvant chemotherapy from T2 to T3. This time interval may have allowed improvement in patients perception of surgical morbidity. And although our sphincter preservation rate was over 80%, patients had to deal with temporary stomas for at least six months.

Finally, we included a late fecal continence evaluation one year after stoma reversal using the Wexner score, which has been recently translated and validated in Portuguese(33). 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. Comparing to basal evaluation(T0), patients improved from general cancer symptoms (Global Health Status), ameliorated on weight loss and constipation, but developed male sexual disfunction. Comparing the late evaluation (T4) to the postoperative period (T2), patients had improvement in role functioning, weight loss, miccional 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”(37, 38). The literature supports the 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(39). Other studies demonstrate stabilization of LARS one year after surgery(40) and that patients after long time follow-up still present significant disfunction (41).

Concerning the specific colorectal cancer module, the 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 were 4 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 and after rectal resection a decrease in 7.8 points in mean scores. The C30SumScore appears to add relevant information to clinical practice allowing comparison between treatment groups and detecting relevant temporal changes in QOL.

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, better body image but more symptoms of constipation. One study from Spain evaluated QOL compared APR versus LAR in 84 patients after neoCRT and Surgery (42). After a mean follow up of 48.7 months, no difference in QLQ-C30 scores was detected. Using the CR29 questionnaire, only stool frequency score was increased in LAR patients (33.3 vs 14.3 points). Another study compared QOL and functional results using Wexner score in 14 patients submitted to ISR versus 22 patients submitted to APR and perineal colostomy(43). 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). 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 (44). 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 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)(44). These suboptimal functional results after curative resection of low rectal cancer motivates investigation of less aggressive approaches to good clinical responders, including the nonoperative management that has been explored in recent literature, including our own institution’s experience(45, 46).

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(47, 48). One tendency in investigation by our group is 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, prevent distant relapse, allows stoma reversal one 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 two years because some stage I and many Stage IV patients were later excluded after ultimate radiological review. Nevertheless, we were able to show 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.

List Of 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

Declarations

Ethical Approval and Consent to participate: this was a prospective study approved by 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.

Availability of supporting data: the datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: all authors declare that they have no conflicts of interests and consented to submit the paper.

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Figures

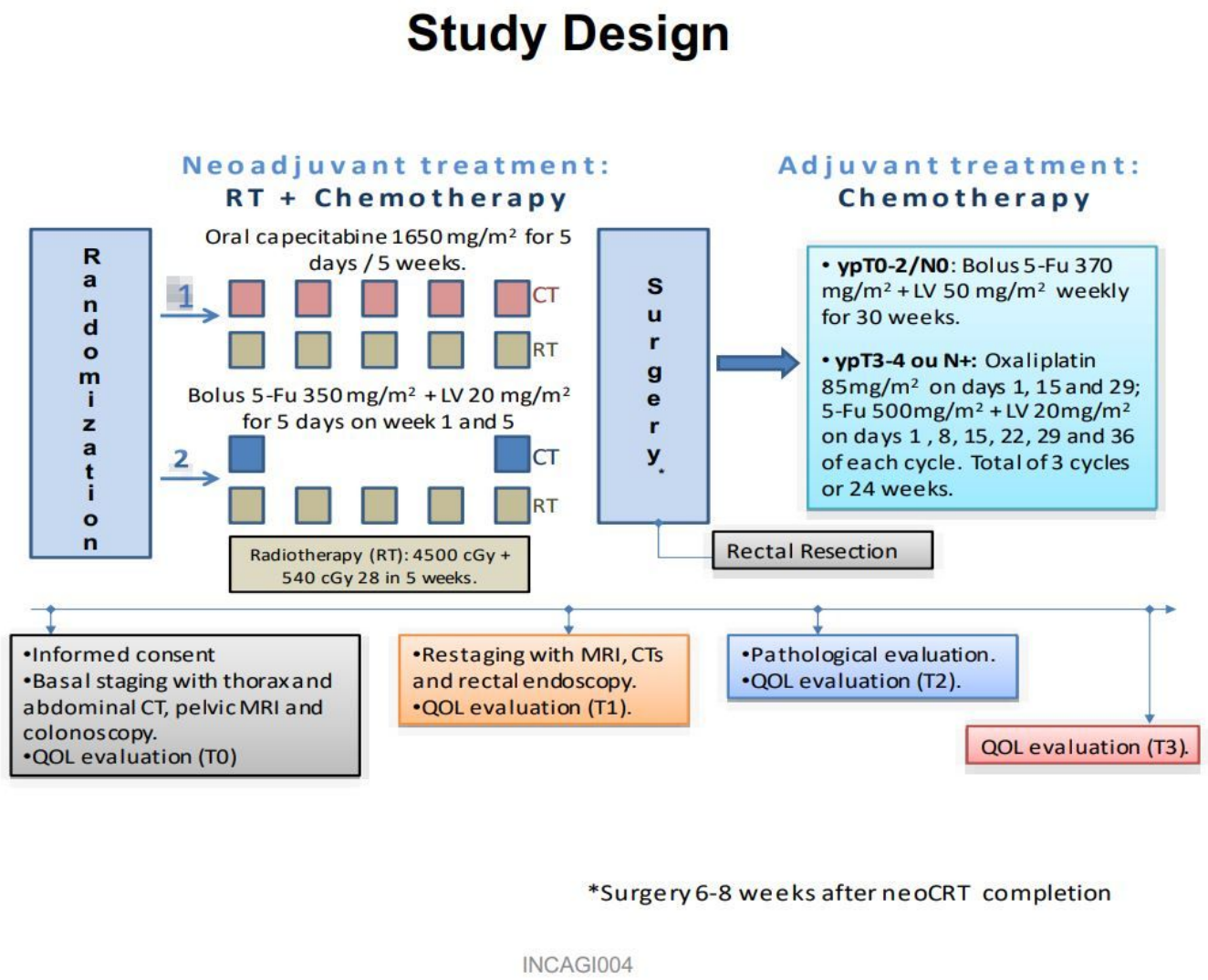

Figure 1

Figure 1 illustrates the study design. Clinical downstaging was the study primary endpoint and was defined as stage regression 6-8 weeks after neoCRT, using AJCC 7th edition(29).

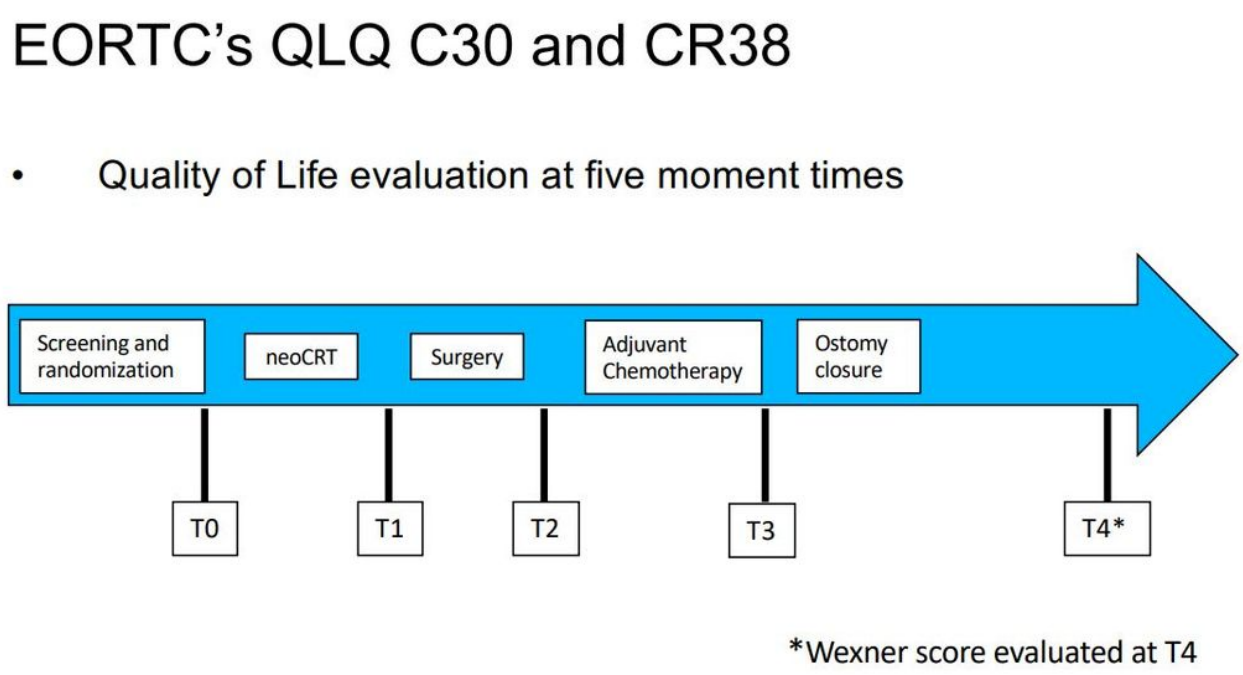

Figure 2

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 one year after the end of the treatment or stoma closure (T4) (Figure 2).

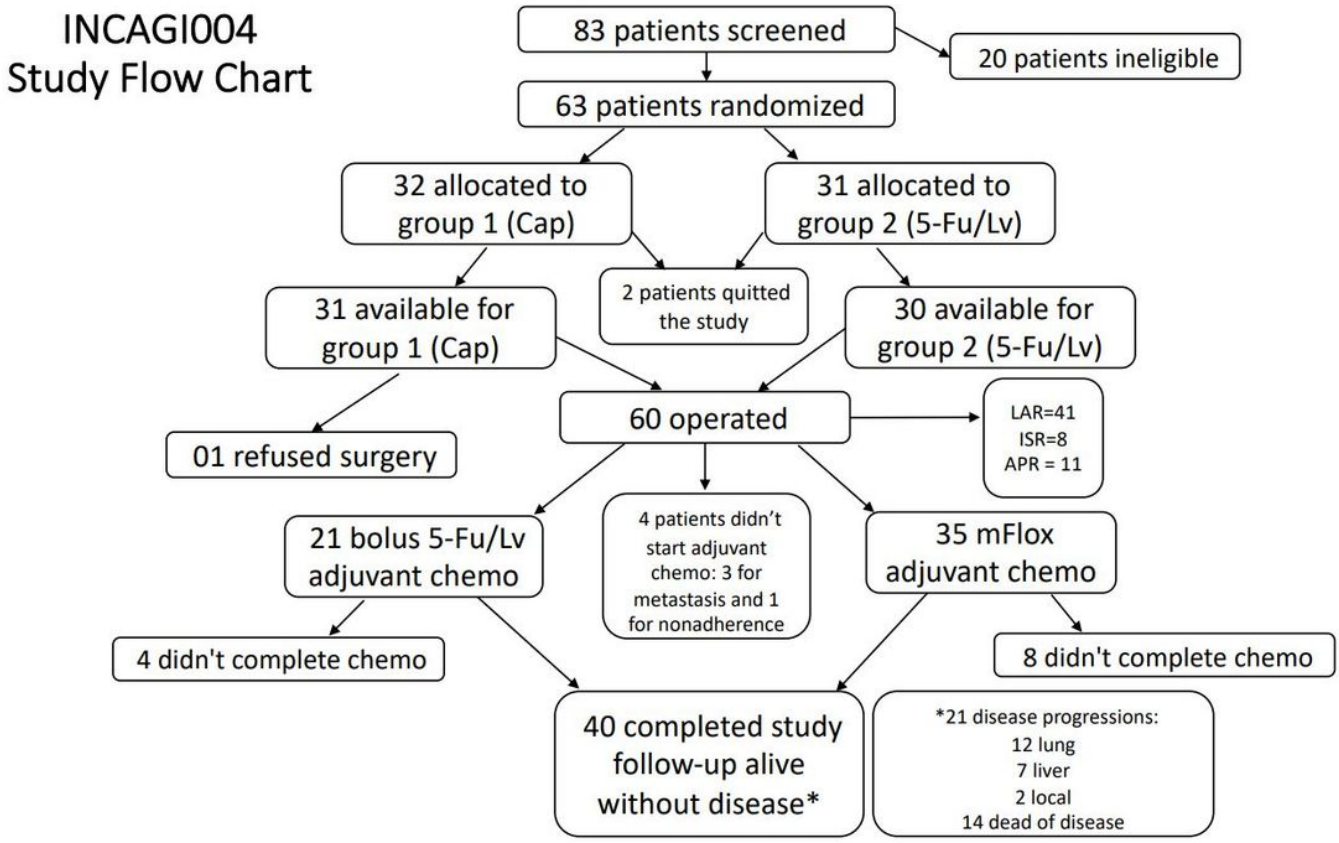

Figure 3

Figure 3 illustrate the study flow chart. Supplementary Table 2 reports the mean C30 and CR38 scores in all domains including the C30SumScore.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1QOL.docx
- SupplementaryTable02.docx
- Graphic1.jpg