Quality of Life Using a Summary Score After Neoadjuvant Treatment and Surgery for Rectal Cancer.

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Abstract

Introduction: Neoadjuvant chemoradiotherapy (neoCRT) followed by surgery is the standard of care for locally advanced rectal cancer (LARC), and sphincter preservation is also an desirable goal, but quality of life (QOL) is often impaired after treatment. **Objective:** To compare QOL in five different moments of treatment in a randomized trial using two different neoadjuvant 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. 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 C30 summary score (Geisinger et cols) was calculated to compare QOL results. **Results:** 32 patients were assigned to Group 1and 31 to Group 2. QOL was improved comparing T0 to T1 (mean 80.5 vs 88.0, $p<0.001$), and decreased comparing T1 to T2 (mean 88.0 vs 80.4, $p<0.001$). No difference in QOL summary was detected comparing T2 to T3 (79.8 vs 82.4, $p=0.194$) or T3 to T4 (83.0 vs 83.0, $p=0.993$). No difference in QOL was detected comparing the two treatment groups. Mean Wexner scale score was 9.2, and a high score correlated with symptoms of diarrhea and defecation problems at T4. **Conclusion:** QOL was improved after NeoCRT but decreased following rectal resection, with no significant recovery during follow-up. Wexner score was high after sphincter preservation. C30 summary score 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.

Introduction:

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]. Neoadjuvant chemo radiotherapy (neoCRT) using 5-fluorouracil (5-Fu) followed by total mesorectal excision (TME) is the standard of care for locally advanced rectal cancer (LARC) resulting in >70% 5-year survival[3,4], but quality of life (QOL) is often disappointing due to temporary stoma creation[5], sexual[6,7] and urinary dysfunction[8], and low anterior resection syndrome (LARS)[8,9].

The EORTC QLQ C30[10] has been used to measure patient reported outcomes, with addition of a specific colorectal cancer module[11]. The Wexner score[12] is used to report fecal incontinence after sphincter preservation as well. Nonetheless, QOL analysis using the multi-item scales leads to conflicting conclusions. Some studies favor sphincter preservation whilst others suggest equivalent or worse results comparing to definitive stoma[13,14]. This may be in part due to the complexity when interpreting results in different domains. In a recent publication, Giesinger *et cols*[15] tested higher order models and proposed a new summary score that could reduce type I errors and sample size requirements.

Objective: To evaluate the quality of life after neoCRT and surgery for LARC in a prospective randomized protocol comparing two drug regimens in five moments of treatment using a EORTC QOL questionnaire and a novel summary score.

Methods:

This study was approved by Ethics Committee of National Cancer Institute of Brazil (INCA) in 2010 under register number 83/10 (NCT03428529). Patients with rectal adenocarcinoma stage II and III and *performance status* ECOG 0-1 were randomized to receive one of the following neoCRT schemes: intravenous bolus 5-Fu (350mg/m^2) plus Leucovorin (20 mg/m^2) days 1 to 5 and 29 to 33; or oral capecitabine 1650mg/m^2 in two daily divided doses from Monday to Friday for five weeks. Both schemes were concomitant to radiotherapy (50.4 Gy in 28 fractions). 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). Surgical resection consisted of low anterior resection (LAR), intersphincteric resection (ISR) or abdominoperineal resection (APR). Clinical downstaging was the study primary endpoint and was defined as stage regression 6-8 weeks after neoCRT, using AJCC 7th edition[16].

EORTC QLQ C30[17] and CR38[18] were applied at five different treatment moments: before neoCRT (T0), 6-8 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). QLQ-C30 questionnaire is composed of 30 questions grouped in nine multiple item scales and six single item scales[13]. 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 of 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. 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[12], 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[19] (Portuguese version[20]) comprises 5 questions for fecal incontinence, producing a score from 0 to 20 and it was accessed at T4.

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%).

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 and the T test to compare continuous variables. Mean differences were considered significant if $p<0.05$ or if a minimum discrepancy of 10 points was found in QOL scales.

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.

Table 1 here

Table 2 reports the mean C30 and CR38 scores in all domains including the C30SumScore. Table 3 shows comparison of QOL scores and the C30SumScore between Group 1 and Group 2 before (T0) and after neoadjuvant treatment (T1). At T0, Group 1 patients reported more constipation and insomnia (> 10 pts mean difference) but reported overall better Global Health Status (p=0.33). After neoadjuvant treatment, no difference in QOL between patients receiving capecitabine or 5-Fu/Lv was shown in any score, including the C30SumScore.

Table 2 here

Table 3 here

We further compared QOL on different moments of treatment (Table 4). After neoCRT (T1) there was a significant improvement in 2 functional scores (Role and Social Function) and reduction in 10 symptom scores (Fatigue, Pain, Appetite Loss, Nausea, Constipation, Diarrhea, GI problems, Weight Loss and Defecation Problems), also reduction in Financial Difficulties and increase in Global Health Status. C30SumScore revealed a mean difference of 7.5 points (mean 80.5 vs 88.0, p<0.001) comparing T1 to T0, favoring overall improvement in QOL after neoCRT. Comparing T1 to T2 after a median time of five weeks (range 3-15 weeks) after surgery there was a decrease in three functional scales scores (Physical, Role and Social) and worsening of symptoms of Fatigue, Appetite Loss, Nausea and Diarrhea, and a decrease of 8 points in C30SumScore (mean 88.0 vs 80.4, p<0.001). C38 scores also demonstrated higher levels of weight loss, CT side effects, male sexual problems, stoma related problems, body image and lower sexual functioning, meaning that QOL worsened in many domains after rectal resection. At T3, after a median time of 11 months after surgery (range 8-22 months), patients had improvement in mean Role Functioning and decrease in Appetite Loss, Weight Loss, and better Sexual Functioning. Nonetheless, C30SumScore Scale didn´t show significant improvement comparing T2 to T3 (79.8 vs 82.4, p=0.194). Comparing T3 to T4 after adjuvant CT and stoma closure, after a median time interval of 39 months after T3 (range 23-52 months) there were higher scores of Constipation and Diarrhea. C30SumScore results were similar comparing T3 and T4 (83.0 vs 83.0, p=0.993).

Table 4 here

Comparing QOL scores after rectal resection (T2) to the late evaluation at T4 (median time interval of 49 months, range 34-60 months), patients referred improvement in Physical and Role Functional Scores, less Fatigue and Constipation and more Diarrhea (Table 5). Global Health Status also improved, but C30SumScore didn´t demonstrate a significant difference. CR38 also demonstrated improvement in Miccional Problems, Weight Loss, Body Image and Sexual Functioning, which corresponds to a general improvement in general aspects of quality of life except for symptoms related to intestinal function (Table 5). Graphic 1 shows temporal changes in QOL using the C30SumScore for each treatment group and for all patients at the five moments of evaluation.

Graphic 1 here.

Table 5 here

Comparing late surviving patients before treatment (T0) versus last follow-up at T4 (after a median time interval of 55 months, range 41-65), patients reported reduction in pain, increased Global Health Status in QLQ C30, but at the end of follow up presented more Chemotherapy Side Effects scores, higher scores on Defecation Problems and Male Sexual Problems, and decrease in Future Perspectives scores.

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 (0-18; 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 6).

Table 6 here

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 balance cure and optimization of the quality of life. 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. We hypothesized that EORTC's QOL scores would reflect clinical differences in disease responses and toxicities according to treatment group results. Comparing QOL results, there were no difference in the two treatment arms in any of the five moments of evaluation. This is in agreement with our clinical response, that was equivalent in the two groups (70.0% in Group 1 vs 53.3% in Group 2, p=0,233), and only one patient suffered from toxicity grade 3 in the neoadjuvant phase. 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[21]. 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[22,23]. Nevertheless, comparing the moments before and after neoCRT we eliminated the interference of surgical resection and oxaliplatin, which allowed a direct comparison of the two drugs in combination to radiotherapy.

We were also concerned with 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, comprising all patients. We have observed that good clinical responders with low rectal cancer close to sphincter complex could have their intestinal continuity reestablished using coloanal anastomosis and/or intersphincteric resection, although functional results were often suboptimal (mean Wexner score of 9.1). Many adaptations in daily routine are needed, and social life is seriously compromised.

Both neoadjuvant schemes were effective in ameliorating general cancer symptoms and health status after CRT(T1) compared to baseline (T0), expressed as improvements in 10 out of 13 scales of QLQ C30 and no worsening of any domain of QLQC30 and CR38 questionnaires. In contrast, the adverse effects of rectal resection in QOL were evident: four of the C30 scales and five of the CR38 scales had worse scores comparing T1 to T2. Not surprisingly, patients had nonsignificant improvement in QOL six months after rectal resection, despite receiving many cycles of adjuvant chemotherapy from

T2 to T3. This time interval may have allowed improvement in patients perception of surgical morbidity.

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[16]. 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. Although our sphincter preservation rate was about 80%, patients had to deal with temporary stomas for at least six months.

Our participants have never fully recovered from the treatment even at late evaluation after a median time interval of 49 months. Although some mean functional scores were slightly better at T4 than basal scores, some specific symptom scales of CR38 were significant worse: chemotherapy side effects, male sexual problems and future perspectives. This finding is not exclusive of our study. A Meta-analysis published in 2015 including 13 studies from 2001 to 2015 comprised data from 1805 patients using QLQ C30 and CR38[24]. 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. CR38 was commonly used in adjunct to C30 to measure specific domains of quality of life in colorectal cancer patients. CR29 emerged later and was in validation when we started our study[25]. One criticism to the CR38 questionnaire is that some questions concerning sexuality are often unanswered; these questions were suppressed or revised in the CR29 version. Indeed, in our study few patients answered questions about sexual

problems (only were 4 available to compare Q0 and Q1) and sexual satisfaction (only 19 of 61 were available).

EORTC QLQ C30 is the most used tool evaluating QOL, but its interpretation is sometimes confusing. It displays 15 scales that could lead to type I errors associated to multiple testing. One strategy is to use a summary score, but the original two-item Global QOL scale may not be comprehensive enough to detect changes between patient groups and/or changes over time. It ignores the other 28 questions and may be subject to a “response shift” phenomenon (dispositional optimism). It has been shown that Global QOL scale could not detect deteriorating QOL in patients with progressive and terminal disease[26]. Different dimensions may change in opposite directions over time, and an aggregate score is desirable to evaluate and compare specific endpoints.

In this scenario a group of authors recently proposed a higher order summary score that performed well in an empirical model fit[1]. It was calculated by the mean of all C30 scales except for Financial Problems Scale and Global QOL scale[4]. This so called 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]. A randomized phase 3 rectal cancer study analyzed over time using C30SumScore compared adjuvant capecitabine versus observation after neoCRT and rectal resection in two moments (T3 and T4). After adjuvant capecitabine (6 months after rectal resection, T3) patients reported worse physical functioning, more symptoms of fatigue and dyspnea, and the C30SumScore detected a significant statistical difference between

patients receiving adjuvant capecitabine vs observation, but not clinically significant (mean 82.3 vs 86.9, p=0.006). All differences resolved at T4 (12 months after surgery).

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 7.5 points in C30SumScore and after rectal resection a decrease in 7.6 points in mean scores. Although it is commonly expected a minimum difference of 10 points in mean scores to be clinically significant, in a high order model that combines the information of 13 scales including multiple item scales, a minimum difference of 5 points seems acceptable. The C30SumScore appears to add relevant information to clinical practice. It produces an intelligible numerical score 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. One study from Spain evaluated QOL compared APR versus LAR in 84 patients after neoCRT and Surgery[28]. After a mean follow up of 48.7 months, no difference in C30 scores was detected. Using the CR29 questionnaire, only stool frequency score was increased in LAR patients (33.3 vs 14.3, p=0.001). 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[29]. ISR patients had worse Physical functioning (84.1 vs 100.0, p=0.044) but less defecation problems compared to perineal colostomy 57.1 vs

90.5, p<0.001). Wexner score was similar between two groups (median 11 in ISF versus 10 in APR), which was also similar 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[30]. They found that Physical functioning was better after LAR and ISR vs APR (82.2 and 80.2 vs 69.9, p=0.028 and 0.026 respectively), but constipation and diarrhea were both more frequent in LAR and ISR compared to APR (p<0.05). ISR had mean higher Wexner score than LAR (12.9 vs 9.5, p=0.0038), a difference that was not detected in our series. A previous study from Illinois, USA, also found better Physical functioning after sphincter preservation in a retrospective study (94.0 vs 87.0, p=0.003) but also more constipation (16.0 vs 8.0, p=0.018) and decreased sexual functioning (27.0 vs 76.0, p<0.0001)[31]. 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[32,33] New strategies are under investigation in order 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[34,35]. One tendency in investigation by our group is the total neoadjuvant treatment, in which all cycles of systemic chemotherapy are delivered before neoCRT and rectal resection (ICAR Trial, ClinicalTrials.gov Identifier: NCT03170115). This strategy is aimed to improve response, increase

compliance rates, prevent distant relapse, and also allows stoma reversal one month after TME.

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.

Declaration of competing interest: All authors declare that they have no conflicts of interests and consented to submit the paper.

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

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