Rectal Cancer after neoadjuvant chemoradiotherapy: analysis of survival, quality of life, and biomarkers associated to response.

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INTRODUCTION

Colorectal cancer is the third most common malignant neoplasm worldwide (1.4 million new cases/year). Neoadjuvant chemoradiotherapy (CRT) using 5-fluorouracil followed by surgical resection including total mesorectal excision (TME) has been considered the standard of care for locally advanced rectal cancer, but capecitabine is a promising oral alternative. Sphincter preservation is a goal in low rectal cancer after good response after CRT, but functional results are still controversial due to possible severe incontinence.

OBJECTIVES

Compare two groups of treatment regarding clinical and pathological response, 5y disease free survival (DFS) and overall survival (OS) in association to clinical variables and relevant biomarkers. Quality of Life (QOL) and incontinence assessment to compare both groups and type of surgery

METHODS

This study was approved by Ethics Committee of National Cancer Institute of Brazil (INCA) in 2010 under register number 83/10.

Eligibility Criteria: Patients with histologically proven locally advanced rectal cancer (cT3-4 or positive regional lymph node) on endorectal ultrasonography (EUS) or pelvic Magnetic Resonance Imaging (MRI) < 10 cm from anal verge (AV) were eligible. Thorax and abdominal computer tomography (CT) exams were taken to rule out distant metastasis.

Treatment Plan: Patients were restaged 6-8 weeks after CRT to evaluate clinical downstage and surgery planning. Surgical resection consisted of low anterior resection (LAR), intersphincteric resection (ISR) or abdominoperineal resection (APR). Patients received adjuvant chemotherapy 30 days after surgical resection: 5-FU/LV 30 weeks if pathological ypT0-2N0 or mFlox three cycles (total 22 weeks) if ypT3-4 or N>0. The 5 years follow-up included clinical visits and CEA every 3 months in the first two years and at six month intervals thereafter until death or progression.

Quality of Life: EORTC QOL C30 and CR38 were applied at five different treatment phases: before CRT (Q0), 6-8 after CRT (Q1), 30 days after surgery (Q2), after adjuvant chemotherapy (Q3), and one year after end of treatment or stoma closure (Q4). Wexner score for fecal incontinence (Portuguese validated version*) was accessed at Q4. Biomarker analysis: Paraffin-embedded tumor specimens will be selected, and 3 µm-thick sections will be cut for immunohistochemical study. The sections will be stained using monoclonal antibodies anti-CDX2, anti-MLH1, anti-MSH2, anti-MSH6 and anti-PMS2 in solution media previously validated for diagnostic in our Pathology Department (DIPAT) and will be examined by a senior pathologist.

Statistical Analysis: The study was designed to test the hypothesis of superiority of capecitabine versus bolus 5-Fu in neoadjuvant CRT regimen, with 5% type I error and 80% power. All statistical analysis was performed using SPSS version 18.0 (SPSS Inc, California, USA). Chi-square tests or Fisher exact tests were used to compare patient characteristics between both arms for categorical variables, and Mann-Whitney test was used to compare quantitative variables.

RESULTS(PRELIMINARY)

A total 63 patients were randomized for treatment between January 2011 and February 2013. All patients completed neoadjuvant treatment plan but one patient refused surgery after a complete clinical response. 31 patients were assigned to neoadjuvant capecitabine and 30 to 5-FU/LV (Group 2). After neoadjuvant CRT 31 (50.8%) of patients showed clinical downstaging, 21 (56.8%) in Group 1 and 16 (43.2%) in Group 2 (p=0.184). Sphincter preservation was possible in 49 patients (81.6%), and there was no difference between groups (83.3 versus 80.0, %p=0.111). Mean hospitalization time was 8.9 days overall, and was similar between groups (8.0 versus 9.7, p=0,714 Mann-Whitney test). 30 patients were submitted to totally laparoscopic resection, 12 were video-assisted or converted to open, and 18 were totally open resection, with no difference in group distribution noted (p=0,837). No postoperative mortality occurred. Ten patients out of 60 had complete pathological response (pCR) and there was no difference between groups. There was a strong association between clinical downstaging and pCR (p=0.005).

Wexner Score: Excluding APR and patients who had early recurrences, 27 patients were evaluated using Wexner with a mean score of 9.2 (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 score above 9 (p=0.415). Patients with Wexner score >9 had more symptoms of diarrhea (p=0.006) and defecatory problems (p=0.004) in QOL scores at T4, and was also found a mean difference of more than 10 points in QOL scores of global health status, sexual function and urinary problems.

Conclusions: Both treatment regimens were well tolerated and all patients completed neoadjuvant CRT. Clinical response was equivalent in two treatment arms as well sphincter preservation. Overall late incontinence score was moderate to high and did not correlate with anastomose level, but was associated to impaired QOL in domains of diarrhea, incontinence, urinary and sexual problems.

Pending Results: QOL analysis is planned to be complete and submitted in 2017. Complete follow up and obtain DFS and OS in both groups in 2018. Biomarker analysis using IHC and PCR for targeted genes are planned to late 2017 and 2018 and these results will be associated to response to neoadjuvant CRT and survival as well.

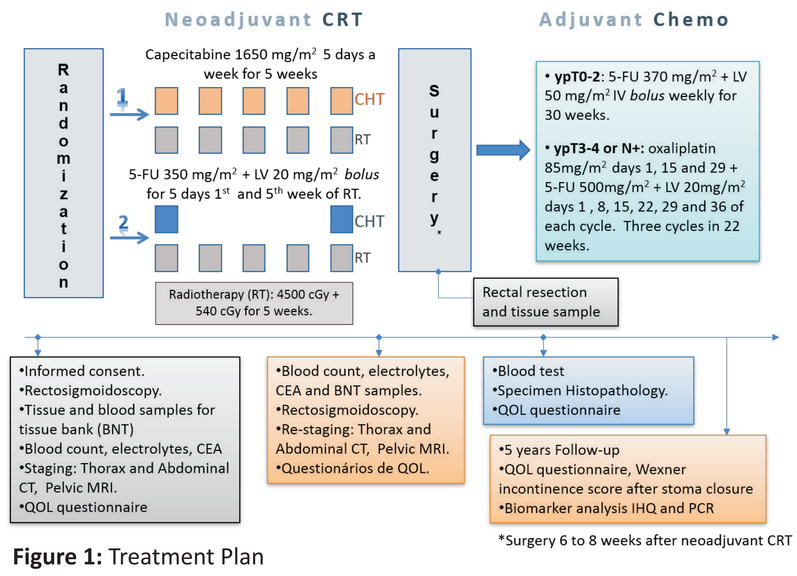


Figure 1: Treatment Plan

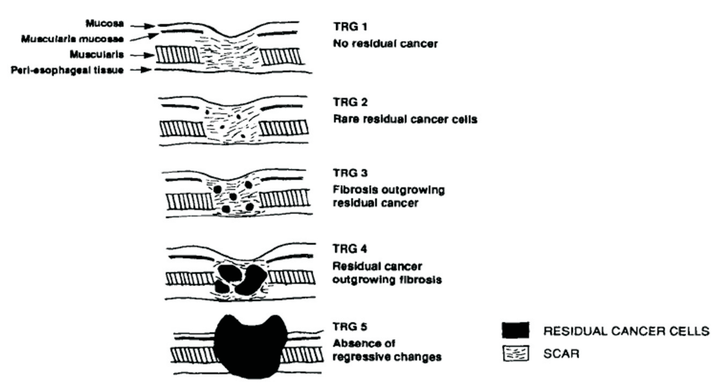


Figure 2: Mandard Classification – Tumor Regression Grade (MANDARD AM *e cols; Cancer* 1994).

Table 1: Patients characteristics

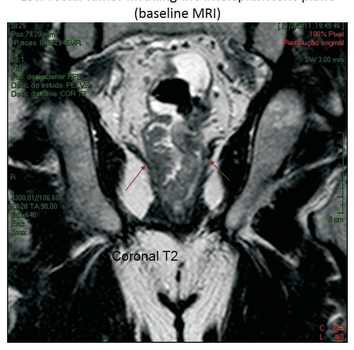
Patients Characteristics	Total N=61 (100%)	Group 1(Cap) N=31 (50%)	Group 2(5-FU) N=30 (50%)	p-value
Gender				
Male	33 (54.1)	16 (51.6)	17 (56.7)	0,692*
Female	28 (45.9)	15 (48.4)	13 (43.3)	
Ethnicity				
White	47 (77.0)	22 (71.0)	25 (83.3)	0,337*
Black	6 (9.8)	3 (9.7)	3 (10.0)	
Mixed	8 (13.1)	6 (19.4)	2 (6.7)	
Age (median)	58	54	60	0,182**
BMI (mean)	26.8	25.8 (18-34)	27.7 (20-38)	0,102**
Tabaco use	34 (55.7)	17(54.8)	17(56.7)	0.886*
PS=1	46 (92%)	24 (96)	22 (95,7)	0,734
CEA basal (med)	4,10	4,06	5,87	0,332
Hg basal (med)	12,4	12,0	12,6	0,541

Cap: capecitabin; 5-FU: 5-Fluorouracil; BMI: Body Mass Index; PS: *Performance Status*; CEA: antígeno carcinoembrionic antigen; Hg: serum hemoglobin.
* Qui-square test
**Anova test

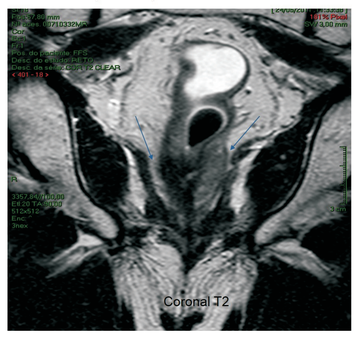
Table 2: Surgical Results

Patients Characteristics	Total N=60 (100%)	Grupo 1(Cap) N=30 (50%)	Grupo 2(5-FU) N=30 (50%)	p-value
Sphincter preservation	49 (81.6)	25 (83.3)	24 (80.0)	0,111
Mean hospitalization	8.9	8.0	9.7	0.714
Access				
VLP	30	16	14	0.356
Video assisted	12	6	6	
Open	18	8	10	
Tumor ≤10 mm AV	14 (28)	4 (16)	10 (40)	0,111
Obstructive tumor	17(34)	9 (36)	8 (33)	0,845

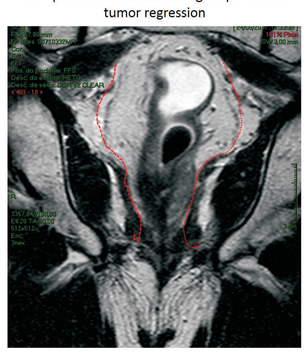
Low rectal tumor invading the intersphincteric plane (baseline MRI)



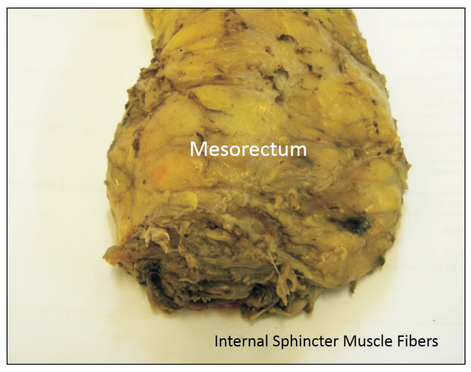
Tumor regression after CRT – no more invasion of intersphincteric plane MRI is noted on MRI



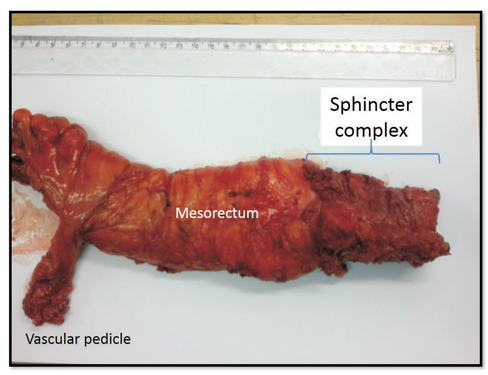
Intersphincteric resection: surgical plane after tumor regression



Surgical Specimen of Intersphincteric Resection - ISR



Surgical Specimen of Abdomino Perineal Resection - APR



Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA