

# RECTAL CANCER AFTER PREOPERATIVE CHEMORADIATION: ANALYSIS OF TUMOR DOWNSTAGING, SPHINCTER PRESERVATION, AND QUALITY OF LIFE IN A RANDOMIZED STUDY COMPARING TWO NEOADJUVANT REGIMENS

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## ABSTRACT

**Introduction:** Colorectal cancer in Brazil is the 3rd most frequent cancer in men and 2nd in woman. Neoadjuvant chemoradiation (CRT) followed by surgery is the standard of care for locally advanced rectal cancer. Capecitabine is an oral alternative to 5-FU, but increased response rates have not been proven. Quality of Life (QOL) after rectal resection is frequently impaired and sphincter preservation can result in poor functional outcomes.

**Objectives:** Access clinical downstaging in rectal cancer after CRT in a randomized study comparing 2 groups of treatment. Evaluate QOL in different phases of treatment and the influence of variables on sphincter preservation.

**Methods:** Patients with rectal adenocarcinoma <10cm from AV, stage II-III and PS ECOG 0-1 were randomized to neoadjuvant capecitabine plus radiotherapy (Group 1) or bolus 5-Fu/Lv plus radiotherapy (50.4Gy)(Group 2). Patients were restaged 6-8 weeks after CRT followed by TME and sphincter preservation when possible. Clinical downstaging was the primary endpoint. Sphincter invasion classified in 5 Grades (adapted from Shihab et al, 2011). EORTC QLQ C30/CR38 was applied at 5 moments and Wexner score was accessed for fecal incontinence.

**Results:** After Institution's Committee approval (NCT03428529) 32 patients were assigned to Group 1 and 31 to Group 2. Clinical downstaging occurred in 58.0% of Group 1 and 60.0% of Group 2 (p=0.543), and was associated to pCR (p=0.005). T stage regression occurred more in Group 1 (35.4% vs 13.3%, p=0.042). Sphincter preservation was possible in 49 patients (81.6%), and correlated to the Grade of sphincter invasion: Grades 0, 1 and 2a had 97.4%, 100.0% and 100.0% preservation compared to 37.5% and 16.0% in Grades 2b and 3 (p>0.001). The probability of achieving a sphincter Grade regression was 48%. T stage regression was associated to sphincter invasion regression (p=0.033). Wexner mean score was 9.2 points (0-18; SD 4.1) and no difference was found comparing Intersphincteric resection to LAR (10.0 vs 9.1, p=0.663). QOL showed overall improvement after CRT but decreased after surgical resection. After stoma closure QOL recovered to pre-treatment levels except from constipation and diarrhea. There were no association between level of anastomosis and incontinence (p=0.415). Patients with Wexner score >9 had more symptoms of diarrhea (p=0.006) and defecatory problems (p=0.004) and was found a mean difference of more than 10 points in QOL scores of global health status, sexual function and urinary problems.

**Conclusions:** Clinical response and sphincter preservation were equivalent but capecitabine induced more T stage regression, which was associated with regression of sphincter invasion. Wexner score was moderate to high and didn't correlate with anastomose level, but was associated to impaired QOL in domains of diarrhea, defecation symptoms, sexual and urinary function.

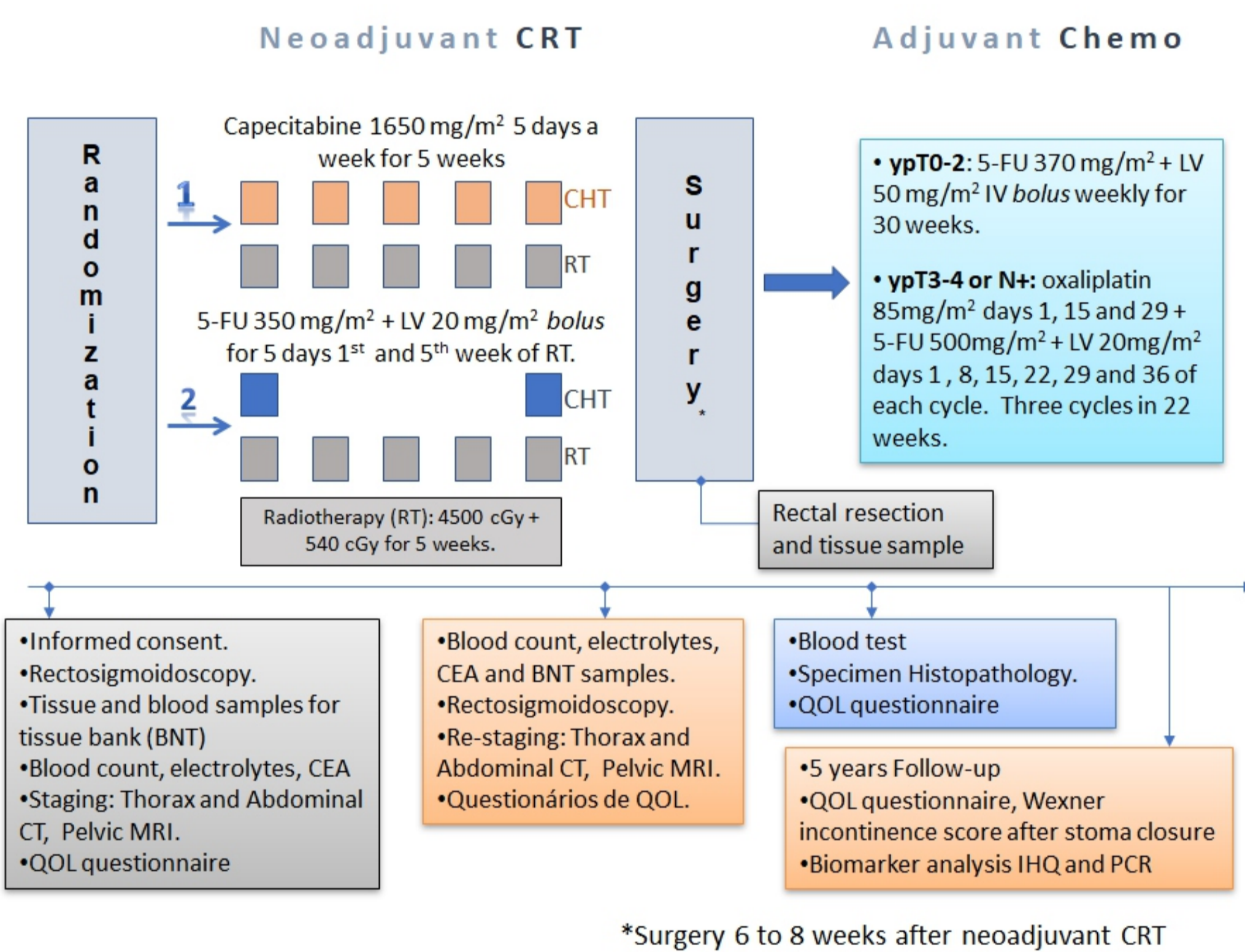


Figure 1: Treatment Plan

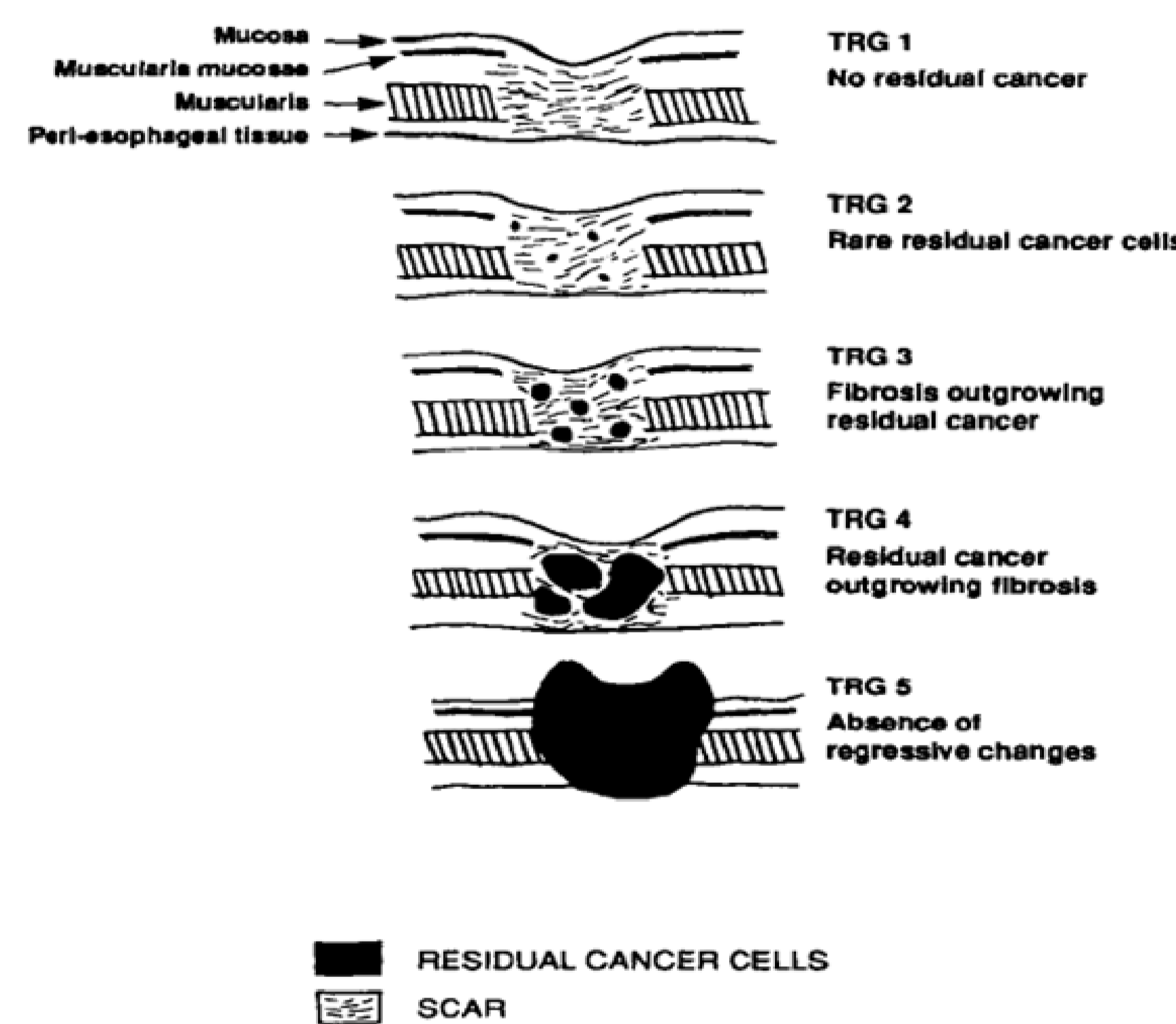


Figure 2. Mandard Classification – Tumor Regression Grade (MANDARD AM e cols; Cancer 1994).

Table 1 : Patients characteristics

Patients	Total N=61 (100%)	Group 1(Cap) N=31 (50%)	Group 2(5-FU) N=30 (50%)	p-value
Male	33 (54.1)	16 (51.6)	17 (56.7)	0,692*
Female	28 (45.9)	15 (48.4)	13 (43.3)	
White	47 (77.0)	22 (71.0)	25 (83.3)	0,337*
Black	6 (9.8)	3 (9.7)	3 (10.0)	
Mixed race	8 (13.1)	6 (19.4)	2 (6.7)	
Age (mean)	58	54	60	0,182***
BMI (median)	26.8	25.8 (18-34)	27.7 (20-38)	0,102**
Cigarette smoking	34 (55.7%)	17(54.8%)	17(56.7%)	0,886*
PS=1	46 (92%)	24 (96%)	22 (95,7%)	0,734*
CEAbasal (mean)	4,10	4,06	5,87	0,332***
Hg basal (mean)	12,4	12,0	12,6	0,541***
Low rectum (<5m AV)	30 (49,2)	14 (46,6)	16 (53,3)	0,612*
Obstructive tumor	21(34,4)	10 (32,2)	11 (36,6)	0,791*

Cap: capecitabine; 5-FU: 5-Fluorouracil; BMI: body mass index; PS: Performance Status; CEA: carcinoembrionic antigen; Hg: serum hemoglobin. \* Qui-square test \*\* Student test \*\*\*Mann-Whitney test

Table 2: Surgical Results

	Total N=60 (100%)	Group 1(Cap) N=30 (50%)	Group 2(5-FU) N=30 (50%)	p-value
Sphincter Preservation	49 (81.6)	25 (83.3)	24 (80.0)	0,111*
Sphincter Preservation (<5cm AV) n=30	20(66.6)	9(64.2%)	11 (68.7%)	1,000*
Length of stay (days)	8.9	8.0	9.7	0,714**
Laparoscopic	30	16	14	
Videoassisted	12	6	6	0,356*
Open	18	8	10	
Surgical Complications	12 (20.0%)	3 (10.0%)	9(30.0%)	0,104*
Medical Complications	9 (15%)	4 (13,3%)	5 (16.6%)	0,726*

Cap: capecitabine; 5-FU: 5-Fluorouracil; AV: anal verge; \* Qui-square test \*\* T de Student test

Table 4: Sphincter preservation after neoadjuvant chemoradiation

Sphincter Invasion Grade	Basal MRI	Sphincter Preservation	CRM+*	Post-treat MRI	Sphincter Preservation	CRM+**
0	36	35 (100%*)	3 (8.3%)	39	38 (97.4%)	4 (9.4)
1	5	4 (80%)	2 (40%)	5	5 (100%)	0 (0)
2a	2	2 (100%)	0 (0)	2	2 (100%)	0 (0)
2b	11	5 (45.4%)	1 (20%)	8	3 (37.5%)	1 (12.5%)
3	7	4 (42.8%)	3(42.8%)	6	1 (16.6%)	4 (66.6%)

\*p=0.123 \*\*p=0.024  
MRI: Magnetic Resonance Imaging  
CRM: circumferential resection margin

Sphincter preservation after neoadjuvant chemoradiation

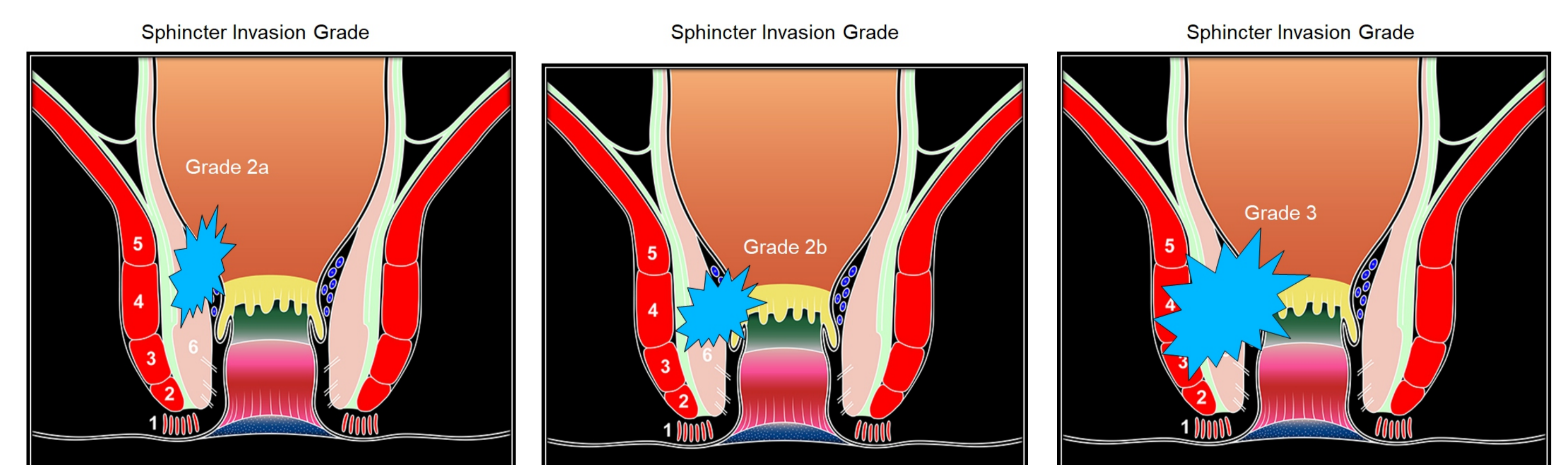
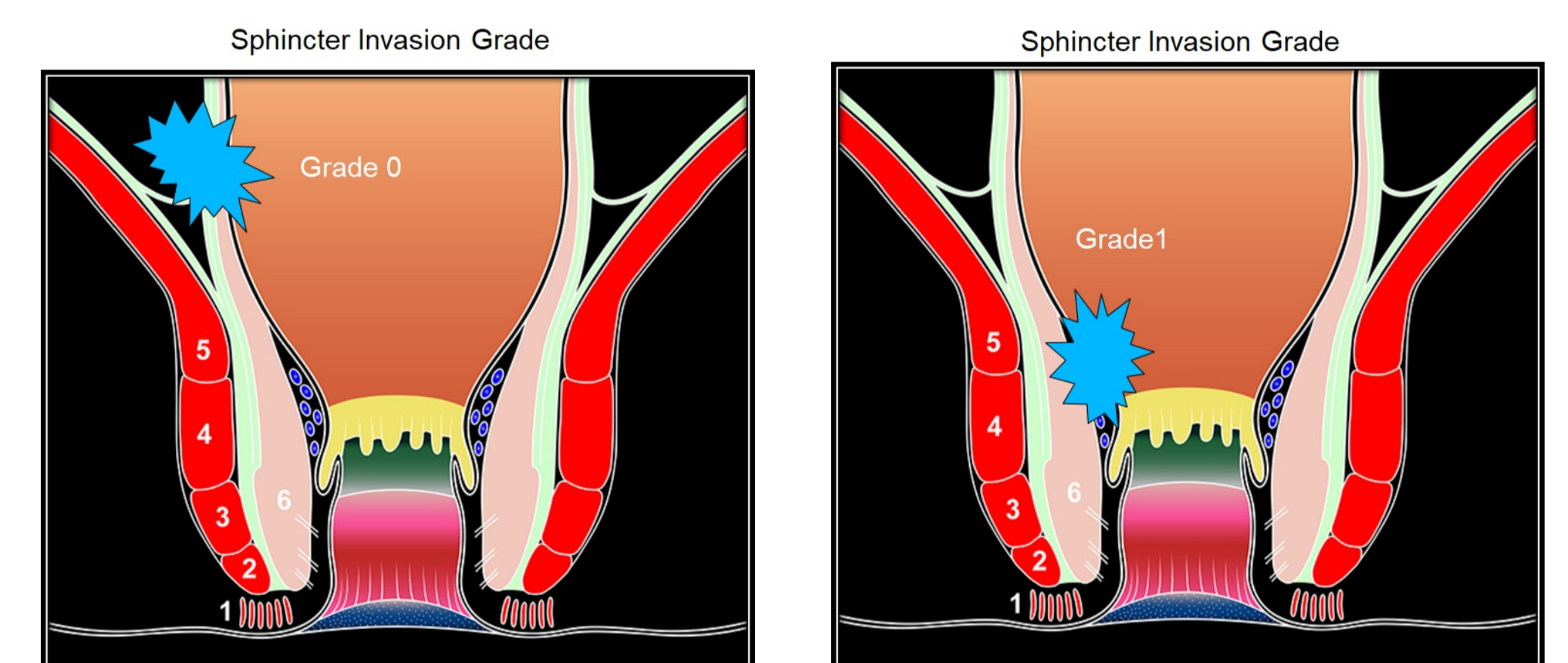


Table 3: Stage Regression

	Total N=61 (100%)	Group 1 Cap N=31	Group 2 5-FU N=30	p-value
Clinical Downstaging	36 (59%)	18 (58.0%)	18 (60.0%)	0,543*
T stage Regression	15 (24%)	11 (35.5%)	4 (13.3%)	0,042*
Sphincter Invasion Regression	9 (14.7%)	3 (9.6%)	6 (20.0%)	0,301*
CRM+	9 (15.0%)	3 (5.0%)	6 (20%)	0,472*
Mandard				0,732**
1	10(16.6)	7(23.3)	3(10.0)	
2	10(16.6)	5(16.6)	5(16.6)	
3	18(30.0)	8(26.6)	10(33.3)	
4	20(33.3)	9(30.0)	11(36.6)	
5	2(3.3)	1(3.3)	1(3.3)	

Cap: capecitabine; 5-FU: 5-Fluorouracil; CRM: circumferential resection margin \* Qui-square test \*\*T de Student