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Treatment Intensification for Locally Advanced Rectal Cancer: Impact on Pathological Complete Response and Outcomes

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Abstract. *Aim: Pathological complete response (pCR) and clinical outcomes [overall survival (OS), disease-free survival (DFS), locoregional control (LC)] were evaluated in a single-institution experience of different schedules of neoadjuvant chemoradiotherapy (CRT) for patients with locally advanced rectal cancer (LARC). Patients and Methods: Data for 322 patients with LARC were retrospectively analyzed. pCR was evaluated according to Mandard tumor regression grade (TRG). The Kaplan-Meier method was used to estimate OS, DFS and LC. Results: Three hundred and three (94.1%) patients underwent surgery. pCR was observed in 81 patients (26.7%), with TRG1-2 rate of 41.8%. The 5- and 10-year OS, DFS and LC rates were 82.5%±2.5% and 65.5%±3.8%, 81.2%±2.4% and 79.3%±2.9%, 93.1%±1.7% and 90.5%±2.1%, respectively. Conclusion: Neoadjuvant CRT in LARC patients resulted in favorable long-term oncological outcomes, with a high pCR rate and acceptable toxicity.*

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Key Words: Chemoradiotherapy, late toxicities, long-term results, rectal cancer, pathological complete response.

Preoperative long-course chemoradiotherapy (CRT) followed by total mesorectal excision (TME) for stage II/III rectal cancer is effective in reducing tumor size, increasing tumor resectability probability and allowing sphincter-saving surgery, with an improvement in the locoregional control (LC) rate (1, 2). In addition, an increased rate of pathological complete response (pCR, *i.e.* the absence of pathological cells in surgical resection) was reported in about 12-15% of patients treated with concurrent fluoropyrimidine (3, 4). Oral capecitabine represents a therapy option and is as well-tolerated, nontoxic and effective in down-staging as 5-fluorouracil for neoadjuvant treatment for locally advanced rectal cancer (LARC) (5-7). Aiming to improve clinical outcomes, during the past two decades, many studies have been conducted to evaluate the impact of treatment intensification in terms of dose escalation or drug combination, with differing results.

Following this evidence, different schedules of CRT have also been utilized at Department of Radiation Oncology of Chieti. We retrospectively analyzed data of patients treated

with neoadjuvant long-course CRT, dividing patients into subgroups according to the different CRT schedules used. We evaluated pCR, and long-term oncological outcomes such as rates of overall (OS) and disease-free (DFS) survival, and LC, estimating factors associated with oncological outcomes.

Patients and Methods

From 2001 to 2019, 322 patients with LARC were treated with preoperative CRT at Department of Radiation Oncology of Chieti and retrospectively analyzed. All patients had histologically confirmed primary adenocarcinoma of the rectum, without extra pelvic disease and staged as cT2-4 N0-2, according to the tumor node metastasis (TNM) staging system (8).

Baseline staging and re-staging after CRT were performed with digital rectal examination and chest-abdominal-pelvic computed tomography (CT) scans, with or without a rectal magnetic resonance imaging (MRI) at least 4 weeks after the end of CRT. RT was performed by 3D conformal technique, with a total dose of 4,500 cGy, 180 cGy/day, to the pelvic nodes, followed by a sequential boost of 540 cGy (180 cGy/day; total dose 5,040 cGy), or a concomitant boost of 1,000 cGy (100 cGy/day, 2 times/week; total dose 5,500 cGy) initially with a 3D-CRT technique and then with simultaneous integrated boost with intensity-modulated radiotherapy (220 cGy/day, total dose 5500 cGy).

During the simulation process, patients were immobilized in the prone position on a belly board, a device aimed at reducing small bowel irradiation, or in the supine position for simultaneous integrated boost with intensity-modulated radiotherapy procedure. The clinical target volume (CTV) included the primary tumor as well as mesorectum, pre-sacral and pelvic nodes up to the L5/S1 junction. In lateral fields, the entire sacrum was included, and the anterior border included the posterior part of the prostate or vagina. Subsequently, the CTV was delineated according to the guidelines available in 2006, including the primary tumor, mesorectum and pelvic subsites (9). The planning target volume (PTV) was the CTV plus 1 cm margin in all directions. Dose was specified according to the International Commission on Radiation Units and Measurements Report 50-62 (10).

Different schedules of drugs were administered as concomitant chemotherapy: 5-Fluorouracil (5-FU) and leucovorin (750-1,000 mg/m^2, continuous infusion from 4 to 5 days) or capecitabine (825 mg/m^2, twice a day for 7 days/week), alone or in association with cisplatin (Plafur: 60 mg/m^2, days 1 and 29, and a 24-h continuous intravenous infusion of 5-FU at 1,000 mg/m^2, days 1-4 and 29-32) or oxaliplatin (Capeox: capecitabine at 1,300 mg/m^2/day, three times/day, for 7 days/week and oxaliplatin at 130 mg/m^2, days 1, 19 and 38). In addition, in patients enrolled in an Italian trial, oxaliplatin was associated with raltitrexed (Tomox: intravenous infusion of raltitrexed at 3 mg/m^2, and oxaliplatin at 130 mg/m^2, 20 min after raltitrexed as a 2-h intravenous infusion, on days 1, 17 and 35) (11, 12).

According to different RT doses and chemotherapy schedules used, we divided our populations into four groups: Fluoropyrimidine chemotherapy plus 50 Gy (fluoropyrimidine group), Plafur chemotherapy plus 50 Gy (Plafur group), Tomox-Capox chemotherapy plus 50 Gy (Tomox-Capox group) and capecitabine with a dose escalation up to 55 Gy corresponding to an equivalent dose at 2 Gy/fraction (EQD2) of 57.5 Gy (considering α/β=5.06 Gy for rectal tumor) (dose intensification group). Radical surgery, including TME, and abdominoperineal resection (APR) or anterior resection, with colorectal or colon-anal anastomosis, was performed according to surgical evaluation.

Considering the distance between the lower pole of the tumor from the anorectal ring, as reported at diagnostic work-up, our patients were split into three subgroups to evaluate possible surgical procedure: Very low location when the distance was <30 mm (candidates for an APR procedure); low location when the distance was 31-50 mm (potential candidates for an APR procedure); and mid-high location when the distance was >50 mm (candidates for a sphincter-saving procedure) (13).

The pathological response was evaluated according to the pTNM pathological classification of the Union for International Cancer Control (8) and tumor regression grade (TRG), based on the Mandard score (14). Tumor regression was classified according to five grades, TRG1 to TRG5, from the best response to the worst, respectively. The absence of residual cancer in the resected specimen (TRG 1) was defined as pCR.

Adjuvant chemotherapy was recommended for patients with positive nodes at pathological examination and for those with T3-4 tumors.

Radiation Therapy Oncology Group (RTOG) toxicity criteria were used to score acute RT toxicities (15). Postoperative routine follow-up examinations were performed every 6 months during the first 5 years from surgery, then annually. Gastrointestinal symptoms and anorectal function of patients were evaluated at baseline and at every follow-up examination. Late toxicities were reported according to the RTOG/European Organization for Research and Treatment of Cancer (EORTC) late RT scoring system (16).

Statistical analysis. All qualitative variables were summarized as frequencies and percentages, whereas all quantitative variables were summarized as the means and standard deviation (SD) or median and interquartile range (IQR) according to their distribution, following the Shapiro-Wilk test.

The Kaplan-Meier method (17) was used to calculate the 5- and 10-year rates of OS, DFS and LC. The follow-up was defined as the time interval between surgery and death due to disease or, for the DFS curve, as the time between surgery and the first verified event; and as the time between surgery and the locoregional recurrence for the LC curve. For patients in whom none of the events occurred, the observational time interval was defined as the period from surgery to the last follow-up visit.

The Kaplan-Meier method was also used to estimate OS, DFS and LC at 5 and 10 years of follow-up after stratifying patients for all other factors. Statistical significance between curves was evaluated using the log-rank test.

A *p*-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using SPSS® software 11.0 (SPSS Inc., Chicago, IL, USA). All research was performed in accordance with the actual version of declaration of Helsinki. No further ethical approval was necessary because this retrospective study was anonymous and non interventional.

Results

Patient population, treatment compliance and acute toxicity. A total of 322 patients were analyzed in this study. Patients, tumor and treatment characteristics are shown in Table I. The median patient age was 65.5 years (range=32-88 years); 209 (64.9%) patients were male. Most patients (80.8%) had cT3 tumors.

Table I. *Tumor, patients and treatment characteristics (n=322).*

Characteristic		Value
Age, years	Median (range)	65.5 (32-88)
Gender, n (%)	Male	209 (64.9%)
	Female	113 (35.1%)
Clinical T-stage, n (%)	T2	33 (10.2%)
	T3	260 (80.8%)
	T4	29 (9%)
Clinical N-stage, n (%)	N0	83 (25.8%)
	N1	156 (48.4%)
	N2	83 (25.8%)
Grade, n (%)	1	42 (13%)
	2	195 (60.6%)
	3	20 (6.2%)
	NOS	23 (6.8%)
	Unknown	44 (13.4%)
Tumor length, mm	Median (range)	50 (6-130)
Distance from anorectal ring, mm	0-30	98 (30.4%)
	31-50	92 (28.6%)
	>50	107 (33.2%)
	Unknown	25 (7.8%)
Chemotherapy schedule	Fluoropyrimidine +45-50 Gy	54 (16.8%)
	Plafur+50 Gy	138 (42.8%)
	Tomox-Capeox+50 Gy	25 (7.8%)
	Capecitabine+>50 Gy	105 (32.6%)
Type of surgery	TEM	9 (2.8%)
	AR	230 (71.5%)
	APR	55 (17%)
	Other	9 (2.8%)
	None	10 (3.1%)
	Unknown	9 (2.8%)
Margin status*	R0	226 (74.6%)
	R1	4 (1.3%)
	Unknown	73 (24.1%)
Pathological T-stage*	T0	72 (23.8%)
	T1	31 (10.2%)
	T2	90 (29.7%)
	T3	106 (35.0%)
	T4	4 (1.3%)
Pathological N-stage*	N0	245 (80.9%)
	N1	46 (15.2%)
	N2	12 (3.9%)
TRG*	1	81 (26.7%)
	2	46 (15.1%)
	3	100 (33%)
	4	69 (22.8%)
	5	5 (1.7%)
	Unknown	2 (0.7%)

Plafur: Cisplatin and 5-fluorouracil; Tomox: raltitrexed and oxaliplatin; Capeox: capecitabine and oxaliplatin; TEM: transanal endoscopic microsurgery; AR: anterior resection; APR: abdominal peritoneal resection; R0: absence of tumor cells in resection margin; R1: tumor cells in resection margin; TRG: tumor resection grade; NOS: not otherwise specified; SD: standard deviation. *N=303.

Table II. *Clinical and pathological stages and type of surgery according to chemoradiotherapy (CRT) regimen.*

	CRT regimen, n			
	Fluoropyrimidine	Plafur	Tomox-Capeox	Dose intensification
Clinical stage pre-CRT (n=322)				
I	3	0	0	1
IIA	17	32	5	19
IIB	1	3	0	2
IIIA	4	12	2	3
IIIB	25	51	14	49
IIIC	4	40	4	31
Surgery (n=303)				
TEM	1	2	0	6
AR	29	107	19	77
APR	14	24	5	10
Other	2	3	0	4
Pathological stage (n=303)*				
ypT0N0	10	17	9	36
ypT0N1	0	2	0	0
0	0	0	0	1
I	17	49	12	29
IIA	13	35	1	13
IIB	0	2	2	0
IIC	0	1	0	0
IIIA	1	4	0	6
IIIB	3	18	0	10
IIIC	2	8	0	2

CRT: Chemoradiotherapy; Plafur: cisplatin and 5-fluorouracil; Tomox: raltitrexed and oxaliplatin; Capeox: capecitabine and oxaliplatin; TEM: transanal endoscopic microsurgery; AR: anterior resection; APR: abdominal peritoneal resection. *According to TNM fifth edition (8).

The majority of patients (139, 43.2%) presented disease of TNM-Union for International Cancer Control stage IIIB, followed by 79 (24.5%) with stage IIIC and 73 (22.7%) with stage IIA. Only 21 (6.6%) patients presented with disease in stage IIIA, four (1.2%) in stage I and four (1.2%) in stage IIB and two (0.6%) stage IIC.

Median tumor length was 50 mm, sited at a distance from the anorectal ring less than 30 mm, between 31 and 50 mm and more than 50 mm in 98 (30.4%), 92 (28.6%) and 107 (33.2%) patients, respectively. Our analysis was conducted on 54 (16.8%) patients in the fluoropyrimidine group, 138 (42.8%) in the Plafur group, 25 (7.8%) in the Tomox-Capeox group and 105 (32.6%) patients in the dose intensification group.

Lower gastrointestinal toxicity was the most frequent acute side-effect experienced: 215 patients (67.7%) had grade 1-2 toxicity, whereas 13 patients experienced grade 3 (4%), as rectal bleeding/severe diarrhea, with one patient (1.9%) in the fluoropyrimidine group, 10 (7.2%) in the

Table III. *Logistic regression predicting tumor resection grade (TRG) 1-2 vs. TRG 3-5.*

Therapy arm	TRG 1-2, n (%)	TRG 3-5, n (%)	Odds ratio (95% confidence interval)	*p*-Value
Fluoropyrimidine	19 (42.2)	26 (57.8)	Reference	-
Plafur	38 (27.9)	98 (72.1)	0.53 (0.26-1.07)	0.076
Tomox-Capeox	13 (54.2)	11 (45.8)	1.61 (0.59-4.40)	0.345
Dose intensification	57 (59.4)	39 (40.6)	2.09 (1.01-4.33)	0.046

Plafur: Cisplatin and 5-fluorouracil; Tomox: raltitrexed and oxaliplatin; Capeox: capecitabine and oxaliplatin.

Plafur group and 2 (1.9%) in the dose intensification group. Skin (humid exfoliation), genitourinary (hematuria) and hematological (anemia) grade 3 toxicities were reported in 11 (3.4%), seven (2.2%) and four (1.2%) patients, respectively. Major acute adverse events occurred in the Plafur group: Nine out of 11 patient (6.5%) experienced skin toxicity, six out of 7 (4.3%) had genitourinary toxicity and three out of four (2.2%) patients had hematological grade 3 toxicity. Eight patients (2.5%) had more than a 10-day break in treatment due to severe toxicities. There were no reported severe neurological and liver toxicities.

Surgery, downstaging and pathologicaI response. Three hundred and three (94.1%) patients underwent surgery.

Anterior resection was performed in 230 patients (71.5%) and APR in 55 (17%) patients. Nine patients (2.8%) with favorable clinical stage (cT2N0) and major pathological response underwent trans-anal endoscopic microsurgery, whereas two patients did not undergo surgery due to their good response observed at the pre-operative re-evaluation. Other surgical techniques were performed in nine (2.8%) patients. Eight (2.5%) patients did not undergo surgery due to being clinically unfit for surgical procedures, or rejection. Data regarding type of surgery were missing for nine (2.8%) patients. Sphincter-saving surgery was possible in 53.7% (29 patients) for the fluoropyrimidine group, 77.5% (107 patients) of the Plafur group and 73.3% (77 patients) for the dose intensification group (Table II).

Sphincter-saving procedure, according to the distance between the lower pole of the tumor and the anorectal ring, was achieved in 60 patients out of 98 (61.2%) in the very low tumor group, 78 out of 92 (84.8%) in the low tumor group, and 83 out of 108 (76.9%) in the mid-high tumor group.

Tumor and nodal-status down-staging was detected in 192 out of 303 patients (63.4%) and in 263 out of 303 patients (86.8%), respectively. Detailed post-neoadjuvant treatment and pathological stages are shown in Table II.

The primary endpoint was the TRG rate: TRG1 was obtained in 81 (26.7%) patients, TGR2 in 46 (15.1%), TRG3 in 100 (33.0%), TRG4 in 69 (22.8%) and TRG5 in five (1.7%) patients; data were missing for two patients (0.7%). Overall, the major pathological response (TRG1-2) rate was 41.8%. The proportion of patients with a TRG1-2 was higher in the dose intensification arm (57 patients, 59.4%) compared to the fluoropyrimidine arm (19 patients, 42.2%), Plafur arm (38 patients, 27.9%) and Tomox-Capeox arm (13 patients, 54.2%), with a statistical significance difference in the dose intensification group (p=0.046) (Table III).

Adjuvant chemotherapy was performed in 89 (30.7%) patients: Systemic fluoropyrimidine-based chemotherapy in 51 (57.3%) and intensification with oxaliplatin in the remaining 38 (42.7%).

Late toxicity and outcomes. The median follow-up was 67.3 months (IQR=34.8-109.6 months). According to the RTOG/EORTC scale, late bowel dysfunction in terms of bleeding requiring surgery (G3 toxicity) was reported in eight patients (2.4%). Mild (five daily bowel movements) and moderate (more than five daily bowel movements) diarrhea were reported in 59 (20.4%) and 25 (8.7%) patients, respectively. No other severe late toxicities were recorded, except for two (0.6%) patients with severe dysuria and one (0.3%) case with gross telangiectasia.

The 5-year OS, DFS and LC rates were 82.5%±2.5%, 81.2%±2.4% and 93.1%±1.7%, respectively. Long-term results at 10 years showed OS, DFS and LC rates of 65.5%±3.8%, 79.3%±2.9%, and 90.5%±2.1%, respectively (Figure 1). OS, DFS and LC rates were not statistically different between the four treatment groups.

Figure 2 shows the 5- and 10-year OS, DFS and LC for patients with TRG1-2 and with TRG3-5. Patients with TRG1-2 had significantly better OS, with 5- and 10-year rates of 85.7% (±3.7%) and 84.2% (±3.9%) compared with 80.1% (±3.2%) and 56.3% (±5.0%), respectively, for patients with TRG3-5 (p=0.001). The 5- and 10-year DFS rates for patients with TRG1-2 were similarly better at 89.5% (±3.2%) and 87.7% (±3.6%) compared with 80.2% (±3.4%) and 73.6% (±4.1%), respectively, for patients with TRG3-5 (p=0.014). The 5- and 10-year LC rates for patients with TRG1-2 were 93.5% (±2.6%) and 91.9% (±2.9%) and did not significantly differ from those with TRG3-5 (Table IV).

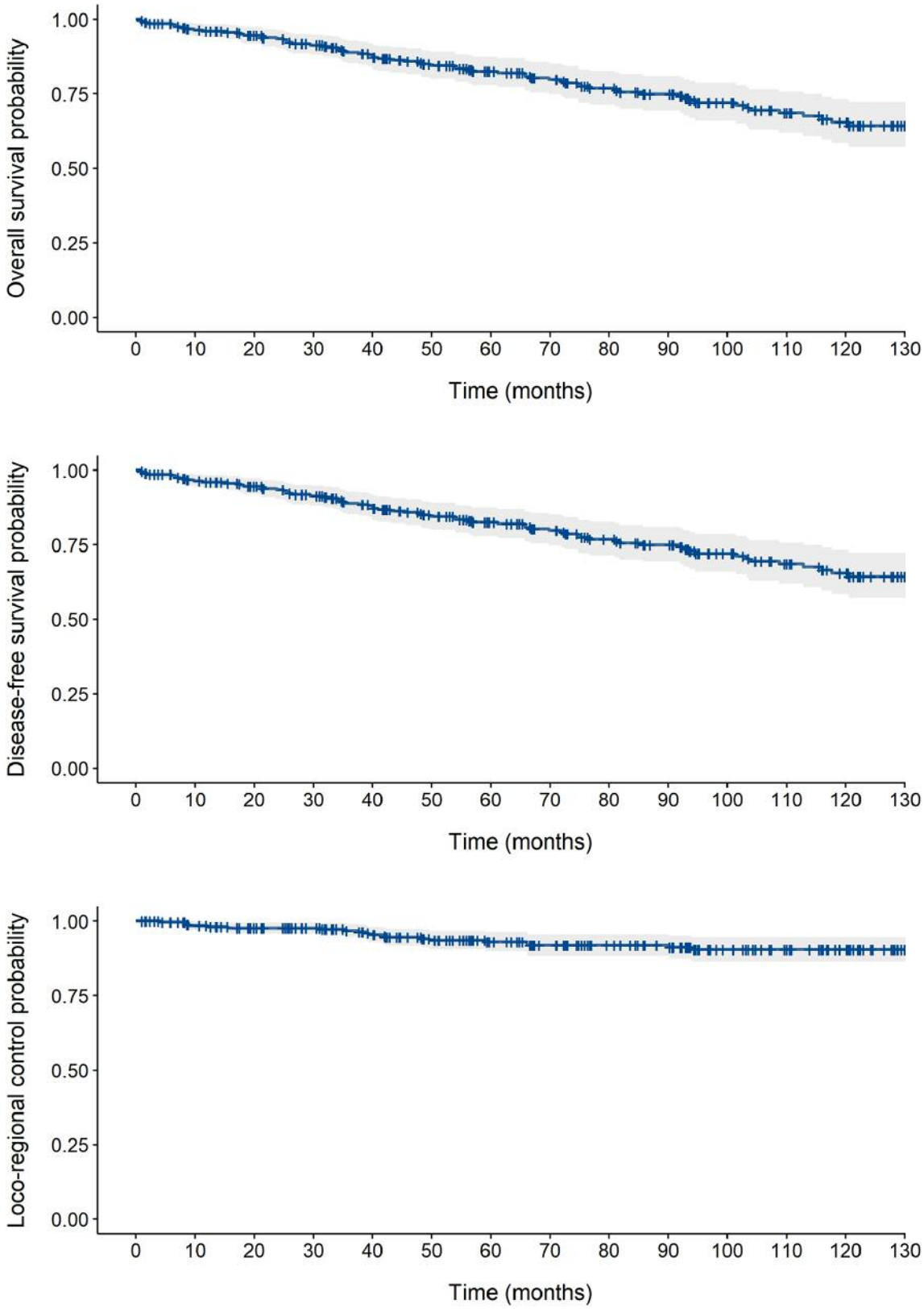

Figure 1. *Kaplan-Meier curves of cumulative overall (A) and (B) disease-free survival as well as locoregional control (C). Tick marks represent cases lost to follow-up and the grey region represents the 95% confidence interval.*

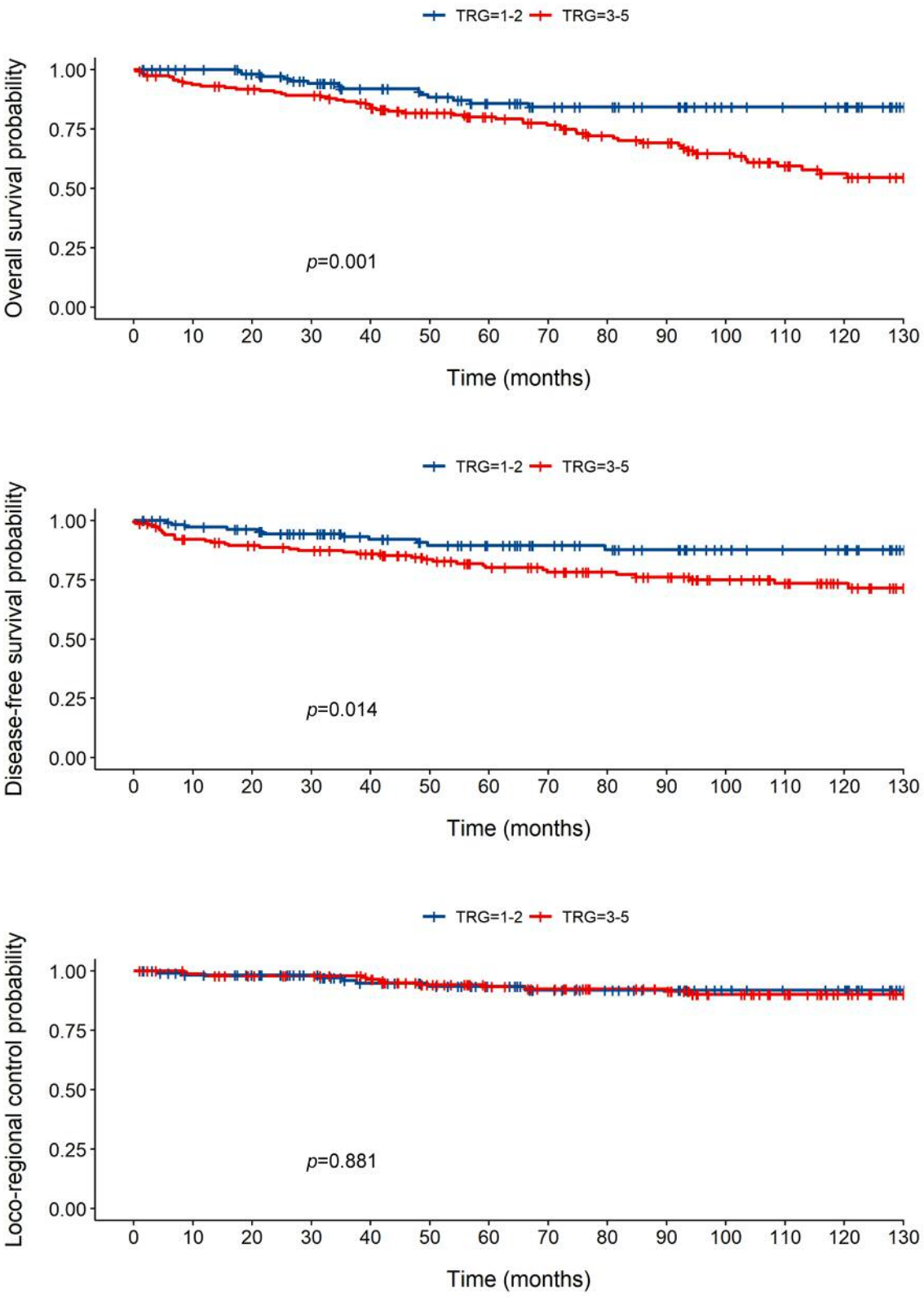

Figure 2. *Kaplan-Meier curves of cumulative overall (A) and (B) disease-free survival as well as locoregional control (C) for patients with tumor regression grade (TRG) 1-2 and those with TRG 3-5. Tick marks represent cases lost to follow-up and the grey region represents the 95% confidence interval.*

Table IV. *Clinical outcomes at 5 and 10 years according to tumor regression grade (TRG) and treatment and tumor parameters.*

	OS				DFS				LC			
	Rate±SE, %				Rate±SE, %				Rate±SE, %			
	5 Years	10 Years	HR (95% CI)	*p*-Value	5 Years	10 Years	HR (95% CI)	*p*-Value	5 Years	10 Years	HR (95% CI)	*p*-Value
Overall	82.5±2.5	65.5±3.8	-	-	84.2±2.4	79.3±2.9	-	-	93.1±1.7	90.5±2.1	-	-
Anorectal ring distance												
0-30 mm	86.0±4.1	58.1±7.4	Reference		77.4±5.2	66.7±6.8	Reference		92.7±3.2	92.7±3.2	Reference	
31-50 mm	75.1±5.0	64.9±6.1	1.02 (0.6-1.8)	0.940	87.8±3.9	83.4±4.8	0.5 (0.2-1.0)	0.051	93.8±3.0	87.4±4.6	1.2 (0.4-3.8)	0.746
≥51 mm	87.3±3.8	74.2±6.2	0.6 (0.3-1.1)	0.094	88.1±3.6	86.2±4.0	0.5 (0.2-0.9)	**0.037**	93.9±2.7	92.3±3.1	0.9 (0.3-3.1)	0.914
TRG												
1-2	85.7±3.7	84.2±3.9	Reference		89.5±3.2	87.7±3.6	Reference		93.5±2.6	91.9±2.9	Reference	
3-5	80.1±3.2	56.3±5.0	2.7 (1.5-4.8)	**0.001**	80.2±3.4	73.6±4.1	2.3 (1.2-4.3)	**0.014**	93.4±2.2	90.2±2.8	1.1 (0.4-2.7)	0.881
CRT												
Fluoropy-rimidine	77.5±7.6	47.9±13.8	Reference		90.0±5.5	90.0±5.5	Reference		96.9±3.1	91.8±5.8	Reference	
Plafur	80.8±3.4	64.6±4.3	0.8 (0.4-1.6)	0.532	81.8±3.4	76.4±8.3	2.2 (0.7-7.3)	0.187	94.6±2.0	91.9±2.5	0.9 (0.2-4.4)	0.951
Tomox-Capeox	95.0±4.9	95.0±4.9	0.2 (0.02-1.3)	0.082	87.7±8.3	87.7±8.3	1.1 (0.2-6.4)	0.951	94.4±5.4	94.4±5.4	0.8 (0.1-8.8)	0.853
Dose intensification	85.2±5.0	NA	0.6 (0.3-1.4)	0.254	83.1±5.8	NA	1.7 (0.5-6.4)	0.405	89.1±4.1	NA	2.1 (0.4-10.2)	0.364

OS: Overall survival; DFS: disease-free survival; LC: locoregional control; Plafur: cisplatin and 5-fluorouracil; Tomox: raltitrexed and oxaliplatin; Capeox: capecitabine and oxaliplatin; NA: not available; CRT: chemoradiotherapy; SE: standard error. Bold values show significance.

Local failure was reported in 25 patients and was peri-anastomotic in 22, pre-sacral in two and pelvic in one; distant metastasis occurred in 55 patients and eight patients had both local and distant progression.

Discussion

The purpose of this retrospective study was to evaluate pCR and long-term outcomes in patients with stage II/III rectal cancer treated with different long-course CRT and TME, with fluoropyrimidine chemotherapy and standard doses of 45-50 Gy, or with an intensification of drugs as cisplatin or oxaliplatin with or without raltitrexed, or with a dose intensification up to 55 Gy.

The locoregional recurrence rate of LARC is about 20%, even with TME. Neoadjuvant CRT is able to improve local control, resectability and pCR rates, as well as to reduce pathological stage (3, 4) (Table V). Capecitabine as a single preoperative concomitant agent was reported to lead to similar downstaging and pCR rates to 5-FU in phase II clinical trials (5, 6), but without statistical differences of OS, DFS and local recurrence rates between capecitabine and 5-FU, resulting instead in an improved pCR rate (14% *vs*. 5%, p=0.009) in the capecitabine arm. This suggested that capecitabine can replace 5-FU in neoadjuvant concomitant chemotherapy for locally advanced rectal cancer (7) (Table V).

The importance of tumor regression assessment in patients with LARC and its relationship with favorable long-term outcomes have been widely reported. Patients with no or few residual cancer cells (TRG1-2) in the pathological specimen after preoperative CRT had improved LC, DFS, and OS, independently of their initial clinical T- and N-stage.

In an Italian retrospective analysis, with 144 patients treated with preoperative CRT for LARC, a TRG1 rate of 19% was reported, with LC, DFS, and OS rates of 87%, 67% and 74%, respectively (18). In the same way, a retrospective multicenter analysis collecting 566 patients with ypCR rate reported predictive favorable outcomes: 5-Year OS of 90%, DFS of 85%, cancer-specific survival rates of 94%, distant metastases in 49 patients (8.9%) and locoregional recurrence in seven patients (1.6%) (19).

Rodel and colleagues assessed the impact of TRG, according to the Dworak classification, as a prognostic factor in 385 patients treated within the preoperative CRT arm of the CAO/ARO/AIO-94 trial. They reported TRG 4, 3, 2, 1, 0 rates of 10.4%, 52.2%, 13.8%, 15.3%, and 8.3% of patients, and complete (TRG4) and intermediate pathologicaI response (TRG2-3) suggested improved DFS after preoperative CRT (20). Based on these and other results (20-22), the pCR rate after CRT in LARC can be considered a surrogate endpoint for DFS and OS.

Table V. *Pathological complete response rate and clinical outcomes in randomized studies of preoperative chemoradiotherapy for rectal cancer.*

Authors and years (Ref)	Patients, n	Concomitant CT drug	pCR (%)	*p*-Value	5-Year OS (%)	*p*-Value	5-Year DFS (%)	*p*-Value	5-Year LR (%)	*p*-Value
Bosset *et al.*	506	RT alone	5.3		64.8		52.2		17.1	
2006 (3)	505	5-FU	14	**0.005**	65.8	0.84	58.2	0.12	7.6	**0.002**
Gerard *et al.*	367	RT alone	3.6		67.9		55.5		13.4	
2006 (4)	375	5-FU	11.4	**0.001**	67.4	0.68	59.4	0.68	6.67	**0.004**
Hofheinz *et al.*	197	Capecitabine	14		76		68		6	
2012 (7)	195	5-FU	5	**0.009**	67	**0.0004**	54	0.35	7	0.67
Gerard *et al.*	299	Capecitabine (Cap45)	13.9		87.6*		67.9*		6.1*	
2010 (30)	299	Capecitabine+ oxaliplatin (Capox50)	19.2	0.09	88.3*		72.7*		4.4*	
Rodel *et al.*	613	5-FU	13		88*		71.2*		4.6*	
2015 (31)	623	5-FU+oxaliplatin	17	**0.031**	88.7*		75.9*	**0.03**	2.9*	
Valentini *et al.*	280	Capecitabine+55 Gy	24.4		80.4		74.7		7.4	
2019 (32)	254	Capecitabine+ oxaliplatin+50.4 Gy	23.8		85.5	0.155	73.8	0.444	6.8	
Current study	322	Different CT drugs	26.7		82.5		81.2		6.9	

CT: Chemotherapy; pCR: pathological complete response; OS: overall survival; DFS: disease-free survival; LR: locoregional relapse; RT: radiotherapy; 5-FU: 5-fluoropyrimidine. *3-Year data. Bold values show significance.

In a pooled analysis conducted by Maas *et al.* on 3,105 included patients, pCR was reported in 484, with 5-year DFS of 83.3% (95% confidence intervaI=78.8-87.0%) for patients with pCR (61/419 patients had disease recurrence) and of 65.6% (63.6-68.0%) for those without pCR (747/2263; hazard ratio=0.44, 95% confidence intervaI=0.34-0.57; $p<0.0001$).The authors concluded that patients with pCR had a prognostically favorable biological tumor profile that significantly increased the probability of DFS (23).

Aiming to improve pCR as well as clinical outcomes, multidrug intensification and dose escalation have been largely investigated (Table V). 5-FU and raltitrexed combined with cisplatin or oxaliplatin and preoperative RT had a safe and effective profile, with high tumor down-staging and pCR rates, in several phase I-II studies (11, 24-26).

A randomized multicenter Italian trial, with 164 patients, reported an overall pCR rate of 30% with a greater rate of TRG1-2 in the Tomox-RT arm compared to the Plafur arm (51.9% *vs.* 41%, $p=0.162$), and a greater rate of ypT0 and significant ypT downstaging ($p=0.035$), even though there was greater acute grade 3 or more toxicity in the Tomox-RT arm (12).

Oxaliplatin plus fluoropyrimidine-based chemotherapy resulted in an improved pCR rate (range=11-42%) in several phase II and III studies, but at the expense of grade 3 or more adverse toxicity without improving clinical outcomes or pCR (27-31).

The German CAO/ARO/AIO-04 phase III trial showed a statistically significant improvement in pCR rate (13% *vs.* 17%, $p=0.038$) and 3-year DFS (75.9% *vs.* 71.2%, $p=0.03$) with the addition of oxaliplatin to 5-FU-based RT (31), although these differences were correlated, according to some author opinions, to the different schedules of 5-FU between the arms.

A multicentric randomized controlled trial was conducted by Valentini *et al.*, investigating two different intensification regimens of preoperative CRT, on 534 patients, 280 treated with capecitabine and a boost dose intensification to 55 Gy, and 254 patients treated with capecitabine and oxaliplatin and 50.4 Gy. The TRG1-2 rates were 61.7% and 52.3% respectively ($p=0.039$) (32).

Our analyses showed a high pCR rate (TRG1-2: 41.8%), with a TRG1-2 of 59.4% in the dose intensification group (EQD2 of 57.5 Gy), similar to that of 61.7% obtained in the capecitabine arm in the INTERACT trial (32). Furthermore, our study found a statistically significant difference ($p=0.046$) comparing TRG1-2 rates in the fluoropyrimidine group with standard dose of 50 Gy (42.2%) compared to the dose intensification group (59.4%) administered a total dose of 57.5 Gy (EQD2). Intensification seems to be attractive in improving clinical outcomes. In contrast, no statistically significant differences were found in clinical outcomes of OS, DFS and LC. In regard to acute and late toxicities, we did not find worse data in the dose intensification group compared to chemotherapy intensification regiments.

A dose-response relationship was confirmed by Burbach *et al.* in a meta-analysis on 18 trials of patients with LARC (33), reporting an improvement of pCR rate up to 20% delivering doses of >6,000 cGy, with acceptable early toxicities. Similar results of dose-response relationships were reported by Appelt *et al.* in 222 patients treated with doses in the range of 50.4-70 Gy (34).

The ability to predict circumferential resection margin involvement using MRI and its correlation with long-term outcomes were also investigated in literature (35). Unfortunately, our study was not able to report these data because of the small number of patients with circumferential resection margin involvement, previously staged by MRI.

Finally, with respect to the relationship between tumor parameters and long-term outcomes, a greater distance from the anorectal ring was reported as a favorable prognostic factor for DFS in the univariate (p=0.037) analyses in our study (Table IV).

In conclusion, neoadjuvant long-course CRT in stage II/III rectal cancer resulted in favorable long-term oncological outcomes, with high pCR rate, tumor and nodal status down-staging, and acceptable toxicity. Dose escalation up to 55 Gy associated with fluoropyrimidine led to a significantly higher TRG1-2 rate of 59.4% (p=0.046) compared to standard doses of 50 Gy with fluoropyrimidine. Moreover, tumor response as TRG1-2 was associated with statistically higher rates of 5- and 10-year OS (p=0.001) and DFS (p=0.014). In our retrospective study, the superior efficacy of dose escalation on major pathological outcome was demonstrated compared to standard dose or multidrug intensification.

Conflicts of Interest

The Authors report no conflicts of interest.

Authors' Contributions

MDT, CR, LC, AA, MT and DG designed and coordinate the study and the analysis. CR, AA, VB, SDS, FP collected the data. MDT, RC, AC, DA, MB, GS, LM reviewed and approved data selection. MDT, CR, LC, MM performed main data analysis and provided pictures elaboration. MM and MDN performed statistical data analysis. MDT, CR, LC drafted the article. MT, PI, PDS, GP, NDB, DG critically revised the study and the article. All Authors reviewed and approved the final article.

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