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Impact of Neoadjuvant Radiochemotherapy on Pathological Complete Response for Locally Advanced Rectal Cancer: A Mono Institutional Experience

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Abstract. *Background/Aim: Neoadjuvant radiochemotherapy followed by surgery is a standard of care in locally advanced rectal cancer (LARC). Only a subgroup of patients can obtain a pathological complete response (pCR) and achieve good local control. However, the role of pCR on patient survival is debated. The aim of the study was to evaluate the impact of pCR on clinical outcomes and toxicities in LARC patients treated with dose intensification and concomitant capecitabine treatment in a neoadjuvant radiochemotherapy schedule. Patients and Methods: This was a single Institution retrospective study including 178 patients. Mandard tumor regression grade (TRG) and pTNM staging system were used to classify pathological response and define pathological complete response (pCR). Patients were divided in: pCR (pT0N0) and Not-pCR (pT>0N>0), according to pTNM and in good responders (TRG1-2) and partial/not responders (TRG3-5), according to Mandard TRG. The Kaplan-Meier method was used to estimate OS, CSS, DFS and LC. Results: A low severe toxicity rate was observed. Acute Grade 3 lower bowel toxicity and Grade 3 cutaneous toxicity were reported in 2 (1.1%) patients, respectively. Late Grade >3 lower bowel toxicity was reported in 6 patients (3%) and late Grade >3 cutaneous toxicity was registered in one patient. No other severe acute and late toxicities were reported. The 5- and 10-year OS, CSS, DFS and LC rates were 85% and 75%, 94% and 92%, 83% and 81%, 88% and 88%, respectively. We observed a pCR rate of 36% and a good responders rate of 62%, in our study population. Both groups showed better rates for each analyzed clinical outcome. Conclusion: Neoadjuvant radiochemotherapy with dose intensification in LARC patients resulted in favorable long-term oncological outcomes, pCR rate showed an optimal impact on OS and DFS with an acceptable toxicity.*

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Colorectal cancer is the third most commonly diagnosed cancer worldwide and the second leading cause of cancer-related death in the world (1). It is estimated that, in Europe, in 2020, colorectal cancer accounted for 12.7% of all new cancer diagnoses and 12.4% of all deaths due to cancer (2). In the same period, in Italy, it is accounted for 11.6% of all new cancer diagnoses and 10.8% of all deaths due to cancer (3). Focusing the attention on the region of central Italy, Abruzzo, where this study was conducted, colorectal cancer was responsible of 14% of all new cancer diagnoses in 2019 (4).

In locally advanced rectal cancer (LARC), comprising T3 and T4 tumors and/or tumors involving locoregional lymph nodes, pre-operative long-course radiochemotherapy (CRT) followed by surgery is now considered a standard of care, since the German CAO/ARO/AIO-94 randomized phase III trial showed a 5-year local control rates of 94%, a higher rate of sphincter preservation and better survival rates (5).

The differences of tumor sensitivity to CRT in LARC patients can lead to differences in responses after the neoadjuvant treatment: from no response to pathological complete response (pCR), defined as the absence of pathological cells in surgical resection. As reported in the literature, pCR is achieved only in 14-20% of patients (6, 7)

and it showed a potential favorable impact on clinical outcomes. In pCR patients, Di Tommaso *et al*. observed 5-year locoregional control (LC), disease free survival (DFS), overall survival (OS) rates of 85.7%, 89.5% and 93.5% respectively (8), and Jalilian *et al*. reported a cancer specific survival (CSS) rate of 94.7% (9). The growing favorable impact on pCR is so interesting that much attention has been paid to non-operative management (NOM), currently only possible within clinical trials (10).

We retrospectively analyzed data of patients treated with radiotherapy (RT) dose intensification and concomitant capecitabine in a neoadjuvant long-course CRT schedule. We evaluated pCR, and long-term oncological outcomes on CSS, OS, DFS and LC.

Patients and Methods

Patients. From 2012 to 2022, 178 LARC patients, admitted to Department of Radiation Oncology of Chieti and treated with preoperative CRT followed by surgery, were retrospectively analyzed. All patients were >18 years old, with histologically confirmed primary rectum adenocarcinoma and without extra pelvic disease [Tumor Node Metastasis (TNM) staging as cT2-4 cN0-2]. Pre-CRT staging with digital rectal examination, chest-abdominal-pelvic computed tomography (CT) scans and with a rectal magnetic resonance imaging (MRI) and re-staging at 8-10 weeks after the end of CRT were performed.

Radiotherapy. RT was performed by volumetric modulated arc therapy (VMAT) technique, with a total dose of 4,500 cGy, 180 cGy/day, to the pelvic nodes and with 5,500 cGy, 220 cGy/day to the whole mesorectum in simultaneous integrated boost (SIB), corresponding to an equivalent dose at 2 Gy/fraction (EQD2) of 57.5 Gy (considering α/β=5.06 Gy for rectal tumor).

During the simulation process, patients were immobilized in the supine position, and it was required to drink 750 ml of water in 45 minutes, in order to obtain an appropriate volume of the bladder. The clinical target volume (CTV) included the primary tumor as well as mesorectum, pre-sacral and pelvic nodes up to the L5/S1 junction. The CTV Boost was delineated including the primary tumor and mesorectum. The planning target volume (PTV) and the PTV Boost was their corresponding CTV plus 8 mm margin in all directions. Dose was specified according to the International Commission on Radiation Units and Measurements Report 50-62.

Concomitant chemotherapy. The drug schedule administered as concomitant chemotherapy was: capecitabine (825 mg/m^2, twice a day for 5 days/week), in no combination with other drugs. Weekly blood tests were performed in all patients.

Surgery. Radical surgery, including anterior resection (AR) with total mesorectal excision (TME) or abdominoperineal resection (APR), with colorectal or colon-anal anastomosis, was performed according to surgical evaluation.

Adjuvant chemotherapy. Adjuvant chemotherapy was administered to 47 patients (26%). Particularly, 39 patients received capecitabine and 4 capecitabine with oxaliplatin, while FOLFIRI with bevacizumab, FOLFIRI with panitunumab, FOLFOX schedules and gemcitabine were given to one patient, respectively.

Pathological response. The pathological response was evaluated according to the pTNM pathological classification of the Union for International Cancer Control and tumor regression grade (TRG), based on the Mandard score (11). 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) and ypT0 was defined as pathological complete response (pCR) (12).

Toxicity. Radiation Therapy Oncology Group (RTOG) toxicity criteria were used to score acute RT toxicities (13). Postoperative routine follow-up examinations were performed every 6 months during the first 5 years from surgery, then annually. Gastrointestinal, urinary, hematological, and cutaneous symptoms were evaluated at baseline, during treatment 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 (13).

Statistical analysis. Descriptive statistics were outlined as frequencies and percentages, whereas all numerical variables as means and standard deviation (SD). Survival analyses for 5- and 10-year rates of OS, CSS, DFS and LC were performed with Kaplan-Meyer analysis. The OS was defined as the time interval between surgery and death; for CSS, instead, the time between the surgery and the death due to the disease. The DFS was considered as the time between surgery and the first verified event (recurrence and/or distant metastasis) and for the LC, the time between surgery and the locoregional recurrence. 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 TRG Mandard Score and for pathological response. A $p<0.05$ was considered statistically significant. The retrospective, anonymous and non-interventional nature of the study did not request any further ethical approval.

Results

A total of 178 patients were analyzed in the study. Patients, tumor, and treatment characteristics are shown in Table I.

The median patient age was 66.3 years (range=37-93 years); 121 (68%) patients were males, with a male/female ratio of 2.2:1. Most patients (85%) had cT3 tumors. All of them underwent the neoadjuvant CRT treatment. Eleven patients interrupted the treatment because of occurred toxicities. Median Follow-up was 42 months (range=2-130 months). During follow-up, 12 (6.7%) patients were lost.

Toxicity. Lower gastrointestinal toxicity was the most frequently experienced acute side-effect: 135 patients (76%) had grade 0-1 toxicity of whom 78 experienced a Grade-1 toxicity. We observed 41 G2 toxicities (23%) and only two

Table I. *Patient characteristics of included patients.*

Characteristic		Value (n)
Age, years	Median, range	66 (37-93)
Sex	Male	121
	Female	57
Clinical T Stage	T2	11
	T3	153
	T4	14
Clinical N Stage	N0	34
	N1	74
	N2	70
Grade	G1	30
	G2	101
	G3	20
	No otherwise specified	17
	Unknown	15
Type of surgery	AR	127
	APR	21
	Other	7
	None	10
Margin status	RO	148
	R1	4
Pathological T stage	T0	58
	T1	11
	T2	49
	T3	47
Pathological N stage	N0	117
	N1	28
	N2	10
Mandard tumor regression grade	1	55
	2	39
	3	40
	4	19
	5	1

patients experienced grade 3 toxicity (1.1%), as rectal bleeding/severe diarrhea. Skin (humid exfoliation) grade 3 toxicities were reported in 2 (1.1%) patients. There were no reported other severe acute toxicities (Table II).

Among late toxicities, bowel dysfunction was reported in 6 patients (3%) of whom 4 patients presented a G4 toxicity skin fibrosis, G4 cutaneous toxicity, were registered in 1 patient. No other ≥G3 toxicity were reported. The most common mild late toxicities (G2) were in lower gastrointestinal and genitourinary tract, and they were shown in 6 (3.6%) and 5 (3%) patients, respectively (Table III).

Surgery. One hundred and sixty-eight (94.4%) patients underwent surgery. Anterior resection was performed in 127 patients (76%) and abdominoperineal surgery in 21 (12.5%) patients. Other surgical techniques were performed in 7 (4%) patients. Ten (5.9%) patients did not undergo surgery due to being clinically unfit for surgical procedures, or rejection. Data regarding type of surgery were missing for 10 (5.6%) patients.

Table II. *Acute toxicities of LARC patients treated with radiotherapy and concomitant capecitabine.*

	G0-1	G2	G3	G4
Lower gastro-intestinal	135 (76%)	41 (23%)	2 (1%)	0
Urinary	173 (97%)	5 (3%)	0	0
Cutaneous	157 (88%)	19 (11%)	2 (1%)	0
Hematological	172 (97%)	6 (3%)	0	0

LARC: Locally advanced rectal cancer.

Table III. *Late toxicities in LARC patients treated with radiotherapy and concomitant capecitabine.*

	G0-1	G2	G3	G4
Lower gastro-intestinal	154 (93%)	6 (4%)	2 (1%)	4 (2%)
Urinary	160 (96%)	5 (3%)	0	1 (1%)
Cutaneous	165 (99%)	0	1 (1%)	0
Hematological	166 (100%)	0	0	0

LARC: Locally advanced rectal cancer.

Pathological response. The primary endpoint was pathological response. Tumor and nodal-status down-staging was detected in 106 out of 168 patients (63%) and in 113 out of 168 patients (67%), respectively. According to pTNM staging system, 58 patients obtained pT0, pT1 in 11 patients, pT2 in 49 patients and pT3 in 47 patients while pN0 was reported in 117 patients, pN1 in 28 patients and pN2 in 10 patients. According the TRG rate: TRG1 was obtained in 55 (35.5%) patients, TGR2 in 39 (25.1%), TRG3 in 40 (25.8%), TRG4 in 19 (12.2%) and TRG5 in only 1 (0.6%) patient. The major pathological response (TRG1-2) rate was 62% (96/155 patients) and the minor or no response (TRG 3-4-5) rate was 38% (59/155 patients). Post-surgery data was missing in 13 patients (7.7%).

Outcomes. The 5-year OS, CSS, DFS and LC rates were 85%, 94%, 83% and 88%, respectively. Long-term results at 10 years showed OS, CSS, DFS and LC rates of 75%, 92%, 81%, and 88%, respectively. Figure 1 and Figure 2 show that patients with TRG1-2 had better OS, with 5- and 10-year rates of 87% and 87% (compared with 81% and 54%, for patients with TRG3-5, respectively) and a better LC with the 5- and 10-year LC rates for TRG1-2 patients of 92% and 92% (*vs*. 83% and 83%, respectively, for patients with TRG3-5). Particularly, in CSS, we observed a better outcome in patients with TRG 1-2 with 5-year and 10-year rate of 95% and 94% *vs*. 95% and 87% in TRG 3-5 group (Figure 3). Regarding DFS, as shown in Figure 4, patients with TRG1-2 showed 5- and 10-year rates of 87% and 87%

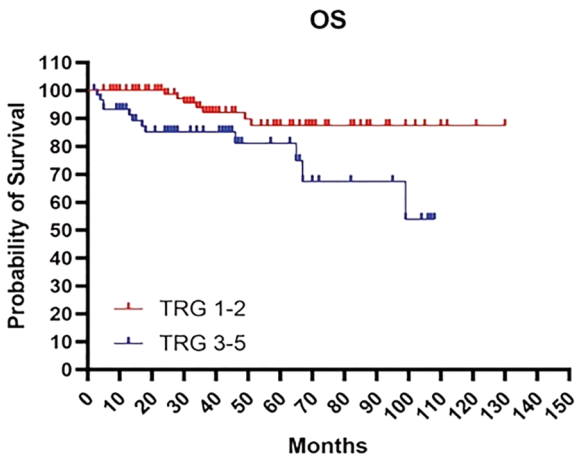

Figure 1. *Kaplan Meier curves for OS in the good-responders group (TRG 1-2) and the partial/no responders group (TRG 3-5). OS: Overall survival.*

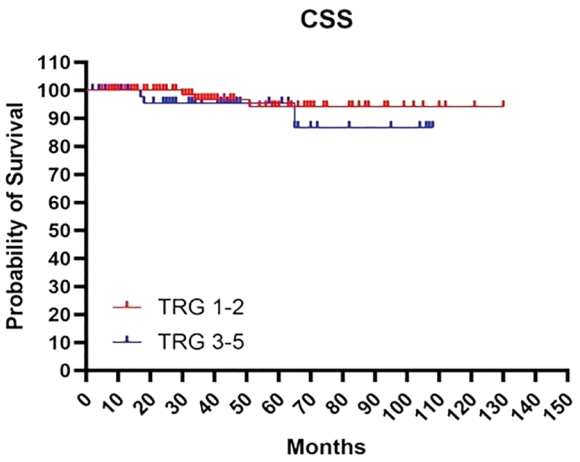

Figure 3. *Kaplan Meier curves for CSS in the good-responders group (TRG 1-2) and the partial/no responders group (TRG 3-5). CSS: Cancer-specific survival.*

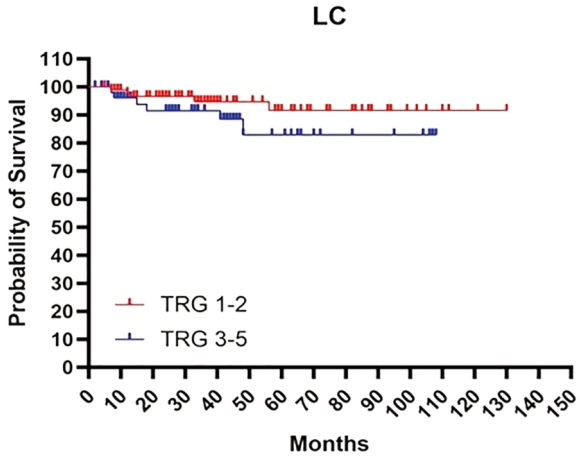

Figure 2. *Kaplan Meier curves for local control LC in the good-responders group (TRG 1-2) and the partial/no responders group (TRG 3-5). LC: Local control.*

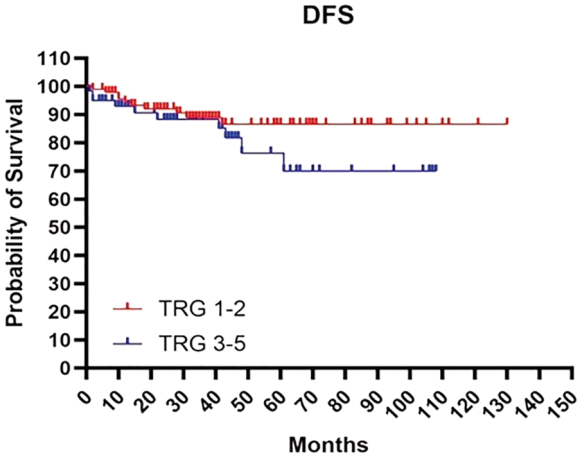

Figure 4. *Kaplan Meier curves for in the good-responders group (TRG 1-2) and in the partial/no responders group (TRG 3-5). DFS: Disease-free survival.*

compared with 76% and 70%, for patients with TRG3-5, respectively. Statistically significance was found in OS analysis (p=0.009).

Analysis about survival outcomes were also conducted in pCR group considered as ypT0pN0. As shown in Figure 5, Figure 6, Figure 7 the rates are higher in this setting of patients compared to the rest of the study population. Five-year OS, CSS and DFS were 89%, 95% and 88% in pCR *vs*. 83%, 95% and 75% in not-pCR group. 10-year OS, CSS and DFS were 89%, 95% and 88% in pCR *vs*. 55%, 86% and 69% in not-p CR group. Even in this setting of patients, statistically significance was found in OS curve: p=0.01.

Discussion

Since the publication of the German CAO/ARO/AIO-94 randomized phase III trial results, preoperative rectal cancer management is the standard of care for LARC owing to its strong control, better clinical survival outcomes and low toxicities. Although a very high loco-regional control can be achieved, there could be the possibility of a systemic pathologic state due to a probable microscopic tumor spread not detected during staging also in patients with a complete or good response. These distant clusters could remain as a source of tumor cells that could lead to the possibility of worse OS and DFS outcomes.

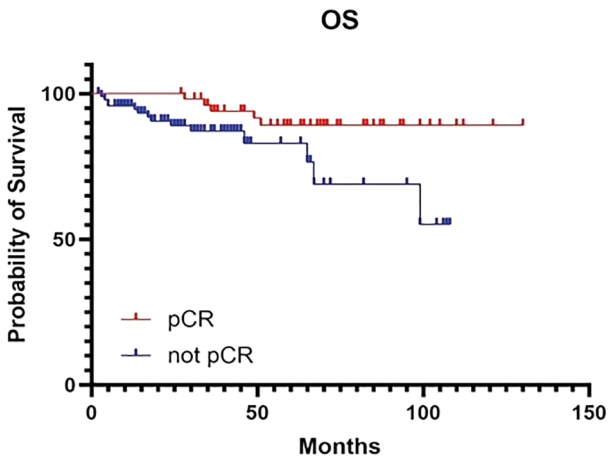

Figure 5. *Kaplan Meier curves for OS in pathological complete the pCR group vs. the not-pCR group. pCR: Pathological complete response, OS: overall survival.*

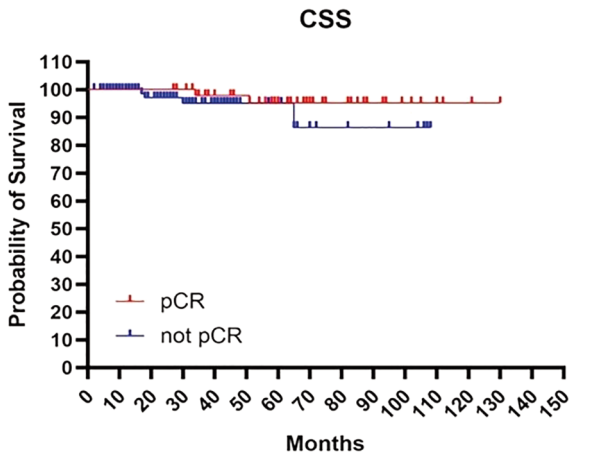

Figure 6. *Kaplan Meier curves for CSS in the pCR group vs. the not-pCR group. CSS: Cancer-specific survival, pCR: pathological complete response.*

Thus, the debate about the benefits of neoadjuvant CRT therapy is still actual, as shown in the recent publication of Tao-Wei Ke *et al*., where the addition of RT in patients with LARC who have undergone only neoadjuvant systemic therapy did not yield statistically significant differences in long-term clinical outcomes (14).

At the same time, neoadjuvant CRT has the potential to determine a good probability of obtaining pCR and with a better quality and life expectancy (5, 15, 16). The concept of the pCR is defined as the absence of tumor cells or the presence of "*in situ* carcinoma" in the resected samples (12). However, there is not a common agreement among literature studies regarding the translation of this definition in the pathologic TNM system. In fact, pCR could be defined as ypT0 or ypT0N0. In our analysis, we chose to describe pCR as anatomo-pathological ypT0N0 report in order to highlight the concept of absence of locoregional disease. All the specimens were also classified according the Mandard TRG Score (9). A TRG 1 was considered as a pCR in agreement with its definition: fibrosis without detectable tumor tissue.

Overall, pCR reported in the literature is between 15-25% (6, 7) in all cases treated with preoperative-CRT but, it can also range from 9% to 30% (17). The role of neoadjuvant CRT combined with surgery in the history of LARC showed its strong benefit in loco-regional control, as showed in a meta-analysis by Martin *et al*. (18) where local control was observed in 99.3% of patients with pCR *vs*. 91.3% in those with non-pCR. Moreover, this meta-analysis also reported better survival outcomes in pCR patients with a 5-year OS and a 5-year DFS rates of 90,2% and 87% respectively (18). Better survival outcomes were also reported in a recent meta-analysis conducted by Li *et al*. in 2021, 12 large studies were

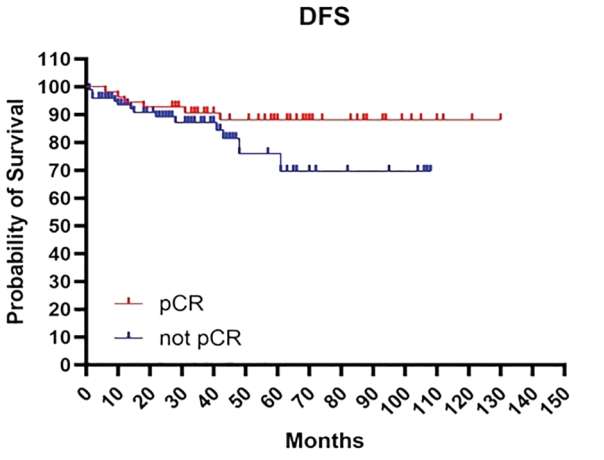

Figure 7. *Kaplan Meier curves for disease-free survival (DFS) in the pCR group vs. the not-pCR group. DFS: Disease-free survival, pCR: pathological complete response.*

selected where 5-year OS and DFS rates in patients with pCR were reported as 93.5% and 90.1% *vs*. 74,4% and 71% in patients with no complete response, respectively (19). Similar to the previously reported findings, Iskander *el al*. (20) reported a 5-year OS and DFS of 94.8% and 88.5% in ypT0N0 patients and Jalilian *et al*. (9) reported a 5-year OS and a DFS of 94.7% and 89.47% respectively in the pCR group with an average follow-up of 74 months. Moreover, in studies reporting 10-year survival results, Sell *et al*. (21) showed that the pCR resulted in survival benefits with a 10-year OS of 86% in the group of pCR patients. In Sakin *et al*. (22) study, the 10-year OS and DFS rates in patients with pCR were 92.3% and 79.4%, respectively.

Table IV. *Comparison of OS and DFS in the "achieved pCR" and "not-achieved pCR" groups.*

	pCR		Not-pCR		pCR		Not-pCR	
Study	5-yr OS	5-yr DFS	5-yr OS	5-yr DFS	10-yr OS	10-yr DFS	10-yr OS	10-yr DFS
Martin *et al*. (18)	90.2%	87%	76%	68%	n.a.	n.a.	n.a.	n.a.
Li *et al*. (19)	93.5%	90.1%	74%	71%	80.5%	n.a	48%	n.a
Iskander *et al*. (20)	94.8%	88.5%	89%*	47%*	n.a.	n.a.	n.a.	n.a.
Jalilian *et al*. (9)	94.7%	89.5%	82.3%	73.5%	n.a.	n.a.	n.a.	n.a.
Sell *et al*. (21)	95%	92%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Sakin *et al*. (22)	92.3%	79.8%	55.8%*	55.7%*	92%	79%	55.8%	51.7%
Our experience	91%	89%	83%	76%	89%	88%	55%	69%

*Rates for no-response patients only. pCR: Pathological complete response; OS: overall survival; DFS: disease-free survival; yr: year; n.a.: not available.

In our study, pCR rate was found to be 36%. The overall loco-regional control was 93% and was observed in 94% of pCR patients, compared with 92% in patients without pCR. The overall 5-year and the 10-year LC rate were 88%. In pCR patients, the rates of both 5- and 10-year LC were 91% *vs*. 85% in no pCR patients. The cumulative OS and DFS rates were 88% and 85%, respectively, in a median follow-up of 4 years. In pCR group, OS was 91% and the DFS was 89%, with a 5-year OS and DFS of 89% and 88% (*vs*. 83% and 76% in not pCR group) and a 10-year OS and DFS of 89% and 88% (*vs*. 55% and 69% in not pCR group), respectively. These results mostly agreed with the cited studies (9, 18-22) (Table IV).

Cancer-specific survival (CSS) is an endpoint very rarely reported in the literature. In their analysis, Jalilian *et al*. (9) reported 14 cancer-related deaths and they observed a cumulative CSS rate of 89% with a pCR impact on CSS of 94.7%. In our study, we observed a CSS rate of 96% with a similar pCR impact on CSS of 97%.

Regarding tumor regression grade prognostic value, in 2005, Vecchio *et al*. (23) observed a correlation between the pathologic tumor response and survival rates in patients receiving preoperative therapy for rectal cancer. As TRG increased, the survival outcomes decreased: 5-year DFS was TRG1: 96%, TRG2: 90%, TRG3: 74%, and TRG4: 52% (p=0.002) and 5-year OS was TRG1: 91%, TRG2: 85%, TRG3: 79%, and TRG4: 63% (p=0.016).

In 2016, Dhadda *et al*. (24) reported that a favorable TRG was associated with better survival rates, showing this parameter as a prognostic factor in their multivariate analysis: 5-years OS and DFS 100% and 95% in TRG1 group; 55% and 50% in TRG 2; and 41% and 33% in TRG 3-5.

In 2020, our previous experience using various long-course neoadjuvant schedules for the impact on TRG confirmed a favorable correlation between TRG and survival outcomes. We selected two groups according the TRG: good responders (TRG 1-2) and poor responders (TRG 3-4-5). Patients with TRG1-2 had significantly better OS, with 5- and 10-year rates of 87% and 87% compared with 84% and 55%, respectively, for patients with TRG3-5 (p=0.001) and the 5- and 10-year DFS rates for patients with TRG1-2 were 89.5% and 87.7% compared with 80.2% and 73.6%, respectively, for patients with TRG3-5 (p=0.014) (8).

As shown in the cited studies, the results of our actual analysis also confirmed the prognostic value of TRG. In fact, patients with complete or partial response (TRG 1-2) reported a 5-year OS and a 5-year DFS of 87% and 87% compared to 5-year OS and a 5-year DFS 81% and 76% respectively, in patients with inadequate response.

The present study had several limitations: it is a mono-institutional study, the sample of the population examined is not particularly large and it is a retrospective study. Furthermore, the Mandard TRG itself requires some considerations: it is only one of the several scores available in literature, such as Dworak, Wheeler and Ryan scores, and each has its peculiar characteristics with regard to possible different clinical interpretations; its sensitivity in terms of difficulty in accurately describing adjacent groups, with differences that could be too subtle to be clinically useful.

Conclusion

An intensification schedule of concurrent neoadjuvant CRT capecitabine-based and SIB of RT on sites of bulky disease in LARC resulted in a positive and significant impact on the pCR (pT0 pN0) with a rate of 36%. Particularly, our study confirmed a very favorable impact of pCR and of TRG1-2 on LC, CSS, DFS and OS at 5 and 10 years with very low acute and late toxicities. In conclusion, our results show that pCR can be considered a valid predictor and neoadjuvant CRT has advantageous long-term outcomes, high pCR rate and tolerable toxicities in daily clinical practice, therefore this schedule can be successfully used in LARC patients.

Conflicts of Interest

The Authors declare no conflicts of interest associated with the study.

Authors' Contributions

Marco Lucarelli and Domenico Genovesi designed and coordinate the study and the analysis. Marco Lucarelli and Virginia Gentile collected the data. Marco Lucarelli, Domenico Genovesi, Rosario Bonelli, Giulia de Pasquale, Andrea Delli Pizzi reviewed and approved data selection. Marco Lucarelli, Marta Di Nicola, Annamaria Porreca performed main data analysis and provided pictures elaboration. Marco Lucarelli, Marta Di Nicola, Annamaria Porreca performed statistical data analysis. Marco Lucarelli, Domenico Genovesi, Rosario Bonelli, Giulia de Pasquale drafted the article. Marco Lucarelli, Domenico Genovesi, Rosario Bonelli, Giulia de Pasquale critically revised the study and the article. All Authors reviewed and approved the final article.

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