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Article

Impact of Dose-Escalated Chemoradiation on Pathological Complete Response in Patients with Locally Advanced Rectal Cancer

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Simple Summary: Approximately 40% of all diagnoses of rectal cancer in Spain are locally advanced. Multi-modal treatment is needed. One of the pillars of their treatment is radiotherapy, with a classic dose scheme of up to 50-50.4Gy concomitantly with oral capecitabine or 5-fluorouracil. Dose escalation is being explored to achieve higher rates of pathological complete response, but the optimal dose and its impact on outcomes are unclear. Our study aims to evaluate the percentage of complete pathological responses obtained with an intensified neoadjuvant radiotherapy treatment scheme. We confirmed in a homogeneous population (49 patients treated with standard radiotherapy vs. 50 patients treated with dose-escalated radiotherapy) higher rates of pathological complete response with a dose up to 54Gy concomitantly with oral capecitabine. Neoadjuvant radiotherapy intensification is useful for specimen sterilization and should be offered to selected patients.

Abstract: Locally advanced rectal cancer requires multimodal treatment. Radiotherapy is being explored for intensification to improve rates of pathological complete responses (ypCR-rates) that correlates with better outcomes. This study reports a comparison between standard versus escalated dose in preoperative scenario. YpCR-rates, toxicity, postoperative complications, disease-free and overall survival at 5 years have been described. From 2012 to 2019, 99 patients were analyzed retrospectively: standard arm (mean 47.5Gy) vs. dose-escalated arm (mean 54.3Gy). All patients were treated with 3DRT in 25 fractions, concomitantly capecitabine and surgery performed according to total mesorectal excision principles in both arms. YpCR was reported by “College of American Pathologist grades”; gastrointestinal (GI) and genitourinary (GU) toxicity using the “Common Terminology Criteria for Adverse Events” (CTCAE 4.0). YpCR-rates were higher in the dose-escalated group (25% vs. 10.64%; $p = 0.07$) with a lower rate of non-treatment response (61.36% vs. 38.64%; $p = 0.11$). No statistical differences between arms were found in terms of oncological outcomes, all postoperative complications ($p = 0.15$), second surgeries ($p = 0.62$), or deaths ($p = 0.62$). CTCAE acute-GI and GU toxicity were grade I or II in both arms. Our study shows that the dose-escalated scheme is safer and obtains higher ypCR-rates.

Keywords: locally advanced rectal cancer; neoadjuvant; chemoradiotherapy; radiotherapy dose escalation; pathological complete response

1. Introduction

Colorectal cancer (CRC) is the most common neoplasm in both sexes in Spain and the second leading cause of specific death, only behind lung cancer. It is estimated that by 2024, 44,294 new cases

will be diagnosed, of which 29,648 will be colon and 14,646 will be rectal, with the average age for CRC diagnosis being around 70 years [1]. Hereditary factors have little impact on the population’s incidence (less than 5% of CRC cases), and most are sporadic tumors with multifactorial etiology. Throughout the disease, 20-25% of patients will develop metastasis, and the overall mortality is around 40-45% [2].

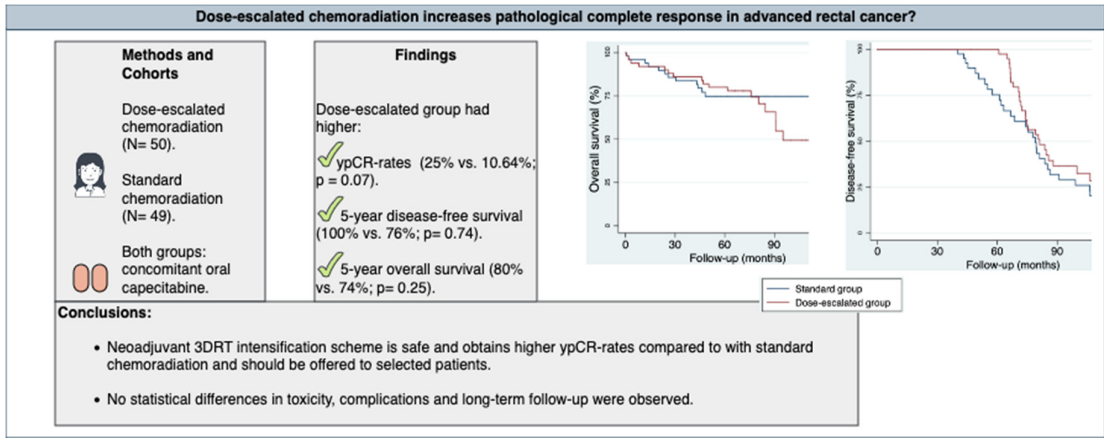


Figure 1. Graphical abstract.

The TNM classification at diagnosis is the most important prognostic factor [3]. Other factors related to survival include the number of lymph nodes resected after surgery (a minimum of 12 [4]), response to neoadjuvant treatment, involvement of the radial resection margin, venous and perineural invasion [5,6], obstructive and/or perforated tumors, grade GIII [7,8], age, carcinoembryonic antigen (CEA) above 20 ng/ml [9], and the patient’s status performance [10,11].

The classic treatment scheme includes preoperative chemoradiotherapy as it reduces pelvic recurrences, controls micrometastases, increases complete response rates to treatment, and improves overall survival by around 10% [12–17]. The standard scheme of RT is conventional fractionation (1.8-2 Gy/fraction/day) up to 50-50.4 Gy combined with capecitabine (CPC) or 5-fluorouracil (5-FU). Complete pathological responses with this treatment scheme are around 20%, and tumor regression is achieved in 40-80% of cases [18–20].

Surgery is the main curative treatment, and the technique of choice is low or ultralow anterior resection with total mesorectal excision (TME), as it preserves the function of the sphincter complex. It is usually performed between 6 and 8 weeks after neoadjuvant treatment [21].

Adjuvant chemotherapy is administered in high-risk stage II or stage III, despite having achieved a complete clinical response, and has shown benefits in DFS. The standard scheme is based on fluoropyrimidines (with or without oxaliplatin) by extrapolation from the data of the ADORE study [22,23], however, it should be individualized assessing the risk/benefit.

Since 2020, following the publication of the RAPIDO study results [24], there are new strategies for neoadjuvant treatment in rectal cancer.

In the RAPIDO trial, patients received 9 cycles of FOLFOX (5-fluorouracil+Oxaliplatin) or 6 of CAPOX (Capecitabine+Oxaliplatin) in a neoadjuvant setting and a short cycle of RT (5 x 5 Gy) before surgery. An ypCR-rate was observed in favor of the experimental arm compared to the arm with 50.4 Gy conventional fractionation + CPC (28% vs. 14%; p< 0.0001). The improvement in local recurrence (LR) and disease-free-survival (DFS) was not statistically significant: LR (7.2% vs. 4.3%; p = 0.20) and DFS (28.5% vs. 24.4%; p = 0.34).

The total neoadjuvant treatment strategy has been explored in another 4 prospective trials: Polish-II [25], TIMING (the only non-randomized one) [26], FOWARC [27], GCR-3 [28], and in a meta-analysis [29]. This strategy improves the rates of complete pathological responses and has proven to be a surrogate factor for DFS [30].

“Watch and wait” or observation after a complete clinical response is not a standard strategy. The decision should arise within a clinical trial or be agreed upon by the multidisciplinary committee in the selected cases. The recommended follow-up in these cases, according to the Habr-Gama et al. protocol [31], should be carried out with anamnesis every 6-10 weeks during the first two years, every 3 months during the third year, and every 6 months from the fourth year, including in all of them: rectal examination, rigid colonoscopy, and determination of CEA levels. In the OPRA study, it was established that patients will undergo rectal examination and flexible proctosigmoidoscopy every 4 months during the first 2 years from the time of response evaluation with magnetic resonance image (MRI) every 6 months in those first 2 years. During the following 3 years, rectal examination and flexible sigmoidoscopy will be repeated every 6 months [32].

Our objective was to retrospectively assess the impact of clinical, histological and outcomes parameters from dose intensification concomitantly with oral capecitabina, and compare rates of pathological complete responses between two different arms of treatment dose.

2. Materials and Methods

Based on a prospective database, a retrospective study was conducted on all patients treated consecutively between June 2012 and December 2019 with neoadjuvant radiotherapy for locally advanced rectal cancer.

Since our study is single-institutional, our series are treated homogeneously with consistent and uniform pathological specimen analysis. Clinicians made the decision on dosimetry jointly with physicians in a daily meeting session based on organ-at-risk limitations.

2.1. Characteristics of the Patients

All patients were evaluated by the multidisciplinary committee for digestive tumors, including the pre-treatment study which consisted of a physical examination, rectal examination, colonoscopy, biopsy, thoracoabdominal-pelvic computerized tomography (CT) scan, abdominopelvic MRI, chest X-ray, complete blood count, and blood tests with tumor markers.

The inclusion criteria were: patients over 18 years old diagnosed with American Joint Committee on Cancer stage II-III rectal adenocarcinoma (classified according to the 6th edition) [33] who had received at least one dose greater than 50.4Gy (considered standard in classic neoadjuvant chemoradiation schemes).

The exclusion criteria were: patients who ultimately did not undergo surgery (due to refusal or high surgical risk), synchronous tumors at diagnosis, and those with a history of other neoplasms.

Patients with LARC were analyzed 1:1 to either a standard treatment arm consisting in preoperative chemoradiation (mean 47.5Gy) or to dose-escalated radiotherapy arm (mean 54.3Gy) as a CONSORT diagram shows in Figure 2.

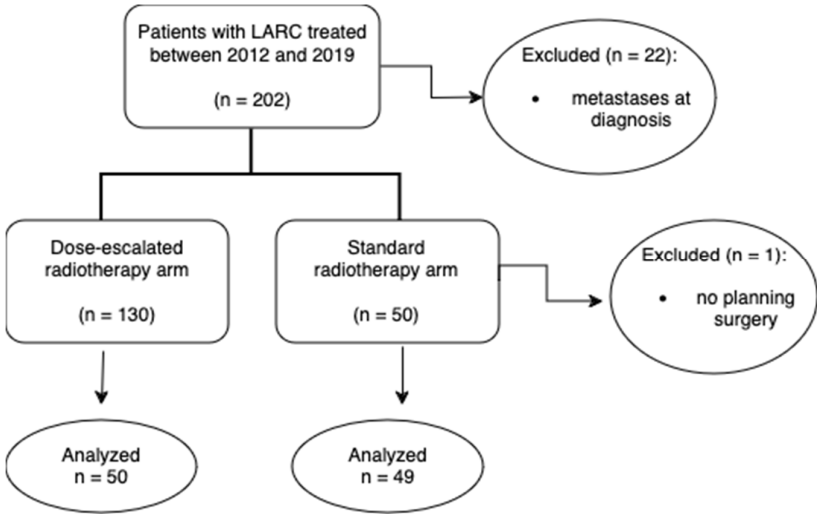


Figure 2. CONSORT diagram of the study.

2.2. Treatment Protocol

2.2.1. Neoadjuvant Chemotherapy

Only 4 patients, those with stage cT4 and/or cN2 at diagnosis and positive extramural invasion, received neoadjuvant chemotherapy. The most commonly used regimens were 1 to 4 cycles of CAPOX. In all cases, the chemotherapy concomitant with radiotherapy was oral CPC at 825 mg/m² every 12 hours on all days that radiotherapy was administered.

2.2.2. Radiotherapy

The patients were immobilized in the supine position with an indexed vacuum mattress, knee support, and arms on the chest [34].

The treatment volumes were defined according to the consensus guidelines for the contouring of gross, clinical and planning tumor volumes structures in anorectal cancer [35].

The upper limit for tumors in the middle-upper third of the rectum was L5-S1, depending on the location of the peritoneal reflection. For tumors in the lower third, the upper limit of the irradiation volume was S1-S2.

The organ-at-risk and the dose limits used are: bladder (V40 < 50%, Dmax < 65Gy), femoral heads (V50 < 5-10%, Dmax < 42Gy), and small intestine (defined in our center as the abdominal cavity 1 cm above the PTV; V40 < 150cc or as close as possible).

The technique used was the “box” type with 3D conformal radiotherapy (0°, 90°, 180° and 270° fields) with a multileaf collimator when the dose went up to 50.4Gy (standard arm). In addition to the “box” technique, lateral fields were modified and oblique fields were added in the boost phase to spare the small bowel when the dose went up to 54 Gy (dose-escalated arm). The planning system used for dose calculation was Pinnacle® from Oracle®. The treatment was performed on a linear accelerator (2100 CD MLC from Varian®) using 6 and 18 MV photons as required by the patient’s anatomy. Daily positioning verifications were carried out for all patients using MV radiographic imaging.

We differentiated two treatment groups: the dose escalation group with a mean of 54.3Gy (IQR 43.4-60.76Gy) in 25 fractions over the tumor and the group that received standard radiotherapy doses with a mean of 47.5Gy (IQR 43.2-50.4Gy) with the same number of total fractions.

2.2.3. Surgery

The response was evaluated using CT or MRI after a minimum interval of about 6 weeks. Only in 8 patients neither of these tests could be performed. In all patients TME was performed. For lower rectal tumors close to the sphincter complex, an abdominoperineal resection (APR) was performed; however, for those with sufficient margin, a low anterior resection was carried out. Hartmann’s procedure was performed in patients with high surgical risk or as a temporary treatment to later perform reconstruction in patients with prolonged surgical time.

2.2.4. Adjuvant chemotherapy

Postoperative chemotherapy was optional based on the pathological features, postoperative and on distant risk factors dissemination. The most commonly used regimens were XELOX and CPC in monotherapy, or both, when oxaliplatin was withdrawn from XELOX due to poor tolerance/toxicity.

2.2.5. Response

During chemoradiotherapy, patients were evaluated weekly; a complete blood count and basic biochemistry were requested biweekly.

As for acute radiation-induced toxicity, data on diarrhea, cystitis, radiodermatitis, abdominal pain, and proctitis were collected and classified according to the CTCAE version 4.0. Likewise,

chronic GI and GU toxicity were recorded starting from the first year after completing treatment, with serial records at the third and fifth years.

The usual follow-up for patients was every 3-4 months during the first two years, every 6 months until the fifth year, and then annually until discharge, which could be up to 10 years. For complementary tests, the recommendations of the ESMO guidelines [11] were followed.

To evaluate the tumor response to chemoradiotherapy, the four-category tumor regression grading (TRG) system developed by the American Joint Committee on Cancer and the College of American Pathologists (AJCC/CAP) was used: TRG 0 (complete response, no tumor cells), TRG 1 (near complete response, isolated cells or small groups of isolated cells), TRG 2 (partial response, residual tumor with evident regression but more groups of cells), TRG 3 (poor or no response, extensive residual tumor with no evidence of regression). The following variables were also collected: lymphovascular, perineural, and extramural vascular invasion and the status of the resection margins (proximal, distal, and circumferential) according to AJCC/TNM R0, R1, and R2, based on whether the resection is clear, microscopically involved, or macroscopically involved, respectively.

Postoperative complications were defined by surgical, infectious, cardiovascular, or other causes, and the need for surgical re-intervention in these patients.

Surgical mortality was defined as that occurring within the first 30 days after the intervention. For the survival analysis, the following variables were defined:

Overall survival (OS). Calculated as the interval of time from the date of surgery, considered the definitive curative intent treatment, to the patient's death from any cause. Patients who were alive at the end of the study were censored at the time of the last follow-up visit.

Disease-free survival (DFS). Calculated as the time from the date of surgery to the date of detection of the first disease relapse and/or death, whichever event occurred first. Patients who were alive and disease-free were censored at the time of the last follow-up visit.

2.3. Statistical Analysis

As measures of central tendency and dispersion for quantitative variables, the median and interquartile range were described, respectively. For categorical variables, frequency statistics such as absolute and relative percentages were used.

We evaluated the association between two categorical variables using the Chi-square method, and if an expected frequency was less than 5, Fisher's exact test was used. In contrast, the association between quantitative variables was evaluated using t-Student tests or analysis of variance (ANOVA), and continuous variables were analyzed with the Mann-Whitney U test. The precision and statistical significance in all cases were at a 95% confidence interval (CI) and a significance level of 5% (p-value < 0.05), respectively.

For the analysis of overall survival and disease-free survival, estimations were made for the entire series and comparisons between patients with different responses to neoadjuvant treatment using the Kaplan-Meier method. The precision and statistical significance in all cases were at a 95% confidence interval (CI) and a significance level of 5% (p-value < 0.05), respectively.

To build the models, a univariate analysis will be conducted where variables with a p-value > 0.10 will be selected for inclusion in the multivariate model. In the multivariate analysis, only variables with a p-value < 0.05 will be considered significant. Data were analyzed using the Stata® statistical software version 14.2 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Characteristics of the Patients

From 2012 to 2019, 99 patients were retrospectively analyzed (standard group: 49, and dose escalation group: 50) with a median follow-up of 5.93 years (IQR 0.03-11.33). The characteristics of the patients by group of treatment are shown in Table 1. The proportions between the treatment arms are similar, indicating that both arms are well-balanced. The variables that influence the achievement of pathological complete responses are analyzed in the present study.

Table 1. Characteristics of the patients.

	Standard arm N= 49	Dose-escalated arm N= 50	p- Value
Age (years)	Median 66.7 (41.1-89.6)	Median 66.2 (40.9-86.7)	0.36
≥ 65y	29 (40.82%)	26 (48%)	0.47
< 65y	20 (59.18%)	24 (52%)	
Gender (female / male)	F = 20 (40.82%) M = 29 (59.18%)	F = 16 (32%) M = 34 (68%)	0.36
Tumor distance from internal anal margin (mm)	Mean = 53.88 0-50 = 13 (26.53%) 51-100 = 24 (48.98%) ≥ 101 = 12 (24.49%)	Mean = 58.6 0-50 = 12 (24%) 51-100 = 25 (50%) ≥ 101 = 13 (26%)	0.53 0.96
cTNM stage	IIA = 6 (12.77%) IIB = 2 (4.26%) IIIA = 4 (8.51%) IIIB = 14 (29.79%) IIIC = 21 (44.68%)	IIA = 5 (10%) IIB = 3 (6%) IIIA = 10 (20%) IIIB = 7 (14%) IIIC = 25 (50%)	0.24
Differentiation Well Moderately Poor	GH I = 39 (81.25%) GH II = 7 (14.58%) GH III = 2 (4.17%)	GH I = 37 (75.51%) GH II = 10 (20.41%) GH III = 2 (4.08%)	0.84
Pretreatment CEA¹ ≥ 5 ng/mL (Yes / No)	Yes = 23 (52.27%) No = 21 (47.73%)	Yes = 21 (42%) No = 29 (58%)	0.32
Pretreatment mesorectal fascia invasion (Yes / No)	Yes = 34 (69.39%) No = 15 (30.61%)	Yes = 30 (61.22%) No = 19 (38.78%)	0.40

¹ CEA: carcinoembryonic antigen.

3.2. Surgery

The surgical procedure par excellence for preserving the sphincter complex is the low anterior resection, which was performed on the majority of patients. The second most performed intervention was the abdominoperineal resection. In only one patient from the dose escalation group, a curative surgery was not performed; instead, due to an ypCR and the advanced age of the patient, a local excision was decided upon. This patient was not included in the disease control and survival analyses as they did not meet the criteria for definitive treatment.

There were no differences between the groups in terms of all postoperative complications ($p = 0.15$), second surgeries ($p = 0.62$), or deaths during postoperative recovery ($p = 0.62$). The most common complication was anastomotic dehiscence or leakage in the dose escalation group, which involved 2 more re-interventions in this group than in the standard dose group ($p = 0.09$). This was followed by paralytic ileus and intra-abdominal collection as the second most common complication in the dose escalation group and the first in the standard group. All paralytic ileus cases, except for one death in the dose escalation group, were resolved with conservative treatment, and the collections were resolved by drainage from interventional radiology. Two patients in the standard group and one in the dose escalation group died within 30 days following the intervention. The causes of death in the standard group were a stroke and persistent anastomotic failure. All complications experienced by the patients can be found in Table 2.

Table 2. Type of complications.

Complications	Standard arm N= 49	Dose-escalated arm N= 50	p- Value
None	53.06 %	46 %	0.48
Wound	2.04 % Hematoma: 1	6 % Hematoma: 1 Infection: 2	0.62
Abdominal	14.29 % Ileus: 4 Collection: 1 Eventration: 2	18 % Ileus: 4 Collection: 4 Abscess: 1	0.62
Urinary tract	6.12 % Uretral injury (iatrogenic): 2 Mictional syndrome: 1	2 % Uretral injury (iatrogenic): 1	0.36
Anastomosis	8.16 % Anastomotic leak: 3 Fistula: 1	22 % Anastomotic leak: 6 Minor drain: 4 Ischemia: 1	0.09
Stoma	2.04 % Sthenosis: 1	2 % Sthenosis: 1 High debit: 1	1.00
Cardiovascular	8.16 % Bleeding: 3 Stroke: 1	2 % Bleeding: 1	0.20
Others	6.12 % Confusional syndrome: 1 Chylous ascites: 1 Neuropathic pain (legs): 1	-	-

3.3. Pathological Response and Downstaging

The dose-escalated group obtained more than double the number of pathological complete responses vs. standard group (25% vs. 10.64%; $p = 0.07$), showing a trend towards significance; and a lower rate of no response to treatment (38.64% vs. 61.36%; $p = 0.11$). In contrast, the rate of responders and non-responders in the standard group is similar. Downstaging was similar in both groups. Variables related to our treatment protocol and the response by groups are shown in Table 3.

Table 3. Variables related to treatment and response.

	Standard arm N= 49	Dose-escalated arm N= 50	p- Value
Completion of treatment			
- Radiotherapy	45 Gy: 24 (48.98 %) 50 Gy: 10 (20.41 %) 50.4 Gy: 13 (26.53 %) Interruptions: 2 (4.08 %)	53.5 Gy: 6 (12 %) 54.25 Gy: 41 (82 %) 60.76Gy: 1 (2 %) Interruptions: 2 (4 %)	0.51
- Chemotherapy	Interruptions: 4 (8.16 %)	Interruptions: 5 (10%)	
Surgery	Saving-sphincter: 33 (67.35 %) Definitive stoma: 15 (30.61 %) Hartmann: 1 (2.04 %)	Saving-sphincter: 33 (66 %) Definitive stoma: 14 (28 %) Hartmann: 2 (4 %) Hemicolectomy: 1 (2 %)	1.00
Time interval (weeks) from chemoradiation to surgery	<8 weeks: 11 (22.45 %) ≥8 to <9 weeks: 7 (14.29 %) ≥9 to <10 weeks: 14 (28.57 %) ≥10 weeks: 17 (34.69 %)	<8 weeks: 8 (16 %) ≥8 to <9 weeks: 9 (18 %) ≥9 to <10 weeks: 15 (30 %) ≥10 weeks: 18 (36 %)	0.85
CAP¹	ypCR = CAP 0: 5 (10.64 %) CAP 1: 16 (34.04 %) CAP 2: 13 (27.66 %) CAP 3: 13 (27.66 %) Unknown: 2	ypCR = CAP 0: 11 (25 %) CAP 1: 16 (36.36 %) CAP 2: 13 (29.55 %) CAP 3: 4 (9.09 %) Unknown: 6	0.07
CAP¹ grouped (responders vs non responders)	CAP 0+1: 21 (44.68%) CAP 2+3: 26 (55.32%)	CAP 0+1: 27 (61.36 %) CAP 2+3: 17 (38.64 %)	0.11
Downstaging	Yes = 40 (81.63 %) No = 9 (18.37 %)	Yes = 44 (88 %) No = 6 (12 %)	0.38

¹ CEA: carcinoembryonic antigen.

3.4. Acute and Chronic Toxicity

Completion of neoadjuvant treatment in both groups was satisfactory and a similar number of patients had interruptions in both groups. The most common cause of interruption was grade III diarrhea, followed by proctitis. There were twice as many interruptions associated with chemotherapy since these patients continued radiotherapy without CPC until resolution. The cases of radiotherapy interruption (2 patients in each arm) corresponded to the non-administration of the last sessions due to grade III diarrhea.

Grade II acute-GI toxicity (according to CTCAE version 4.0) was lower in the standard group (16.33% vs. 24%; $p = 0.06$). Only 4 patients (8%) in the dose escalation group experienced grade III acute gastrointestinal toxicity, and none in the standard group. Grade II acute GU toxicity was lower in the standard group than in the dose escalation group (6.12% vs. 8%; $p = 0.39$). No patient experienced a higher grade of toxicity. Grade I GI toxicity at 3 years was lower in the standard group (12% vs. 18%; $p = 0.25$). Only 2 patients (4.55%) had grade II, and 1 patient (2.27%) had grade III in the dose escalation group. Most patients in both groups were asymptomatic at 3 years in terms of GU toxicity (97.62% vs. 95.45%; $p = 1.00$).

3.5. Bivariable and Multivariate Analysis

The variables analyzed were: age, sex, tumor distance from the anal margin, tumor size (cT) and number of positive lymph nodes (cN), histological grade and CEA at diagnosis, tumor distance to the mesorectal fascia (measured by MRI at diagnosis), and the interval of time from neoadjuvant therapy to surgery.

In the bivariable analysis, we found that for achieving a complete pathological response, smaller tumor size (cT2) is the most favorable factor ($p = 0.01$). Although the RT dose did not reach statistical significance, its OR (Table 4) shows that with dose escalation, more than double the complete pathological responses can be obtained compared to the standard dose (25% vs. 10.64%), not being statistically significant due to the sample size limitation ($p = 0.07$). Since only one variable reached statistical significance, no further multivariate analysis was performed.

Table 4. Variables related to treatment and response.

	p-Value	Odds ratio	IC 95% inferior	IC 95% superior
Age (years)	0.79	1.00	0.96	1.06
Gender (male vs female)	0.64	1.27	0.40	4.00
Tumor location: middle vs inferior superior vs inferior	0.82 0.87 0.71	 0.90 1.31	 0.24 0.31	 3.41 5.60
cT stage: cT3 vs cT2 cT4 vs cT2	0.01 0.01 0.78	 0.16 0.83	 0.04 0.23	 0.66 3.07
cN stage: cN1 vs cN0 cN2 vs cN0	0.46 0.39 0.96	 2.07 1.05	 0.39 0.19	 11.11 5.82
cTNM (reference: stage 0) IIB IIIA IIIB IIIC	0.67 0.55 0.25 0.47 0.72	 2.5 4 2.35 1.5	 0.12 0.38 0.23 0.16	 50.44 42.37 24.09 13.92
Differentiation: HG ¹ II vs HG I	0.96	1.04	0.26	4.14
Pretreatment CEA ² ≥ 5 ng/mL (Yes vs No)	0.25	0.51	0.16	1.64
Pretreatment mesorectal fascia invasion (Yes vs No)	0.36	1.73	0.51	5.85
Weeks from chemoradiation to surgery (reference: < 8) ≥8 to <9 ≥9 to <10 ≥10	0.78 0.86 0.34 0.52	 1.21 2.32 1.76	 0.15 0.41 0.32	 9.76 12.96 9.71
Dose of RT: >50.4 Gy	0.11	2.48	0.79	7.77

¹ HG: histological grade. ² CEA: carcinoembryonic antigen.

3.6. Control and Survival

The 5-year disease-free survival was higher in the dose escalation group than in the standard group (87.6% vs. 64%; $p = 0.82$), as was the 5-year overall survival (81.6% vs. 74.6%; $p = 0.32$) [Figures 1 and 2]. However, we did not find a benefit in terms of outcomes despite achieving higher rates of pathological complete response with a median follow-up of 5.93 years (IQR 0.03-11.33). Local control was similar in both groups (Figure 3). Only 3 local recurrences were documented in the entire series: 1 in the dose escalation group founded outside the irradiation field, and 2 recurrences in the standard group located within the irradiation field. Nine distant recurrences were reported in each group. Regarding patients who achieved an ypCR, only 2 of them died from rectal cancer. Concerning recurrences in patients with ypCR, only 2 patients had a distant recurrence, and none had a locoregional recurrence.

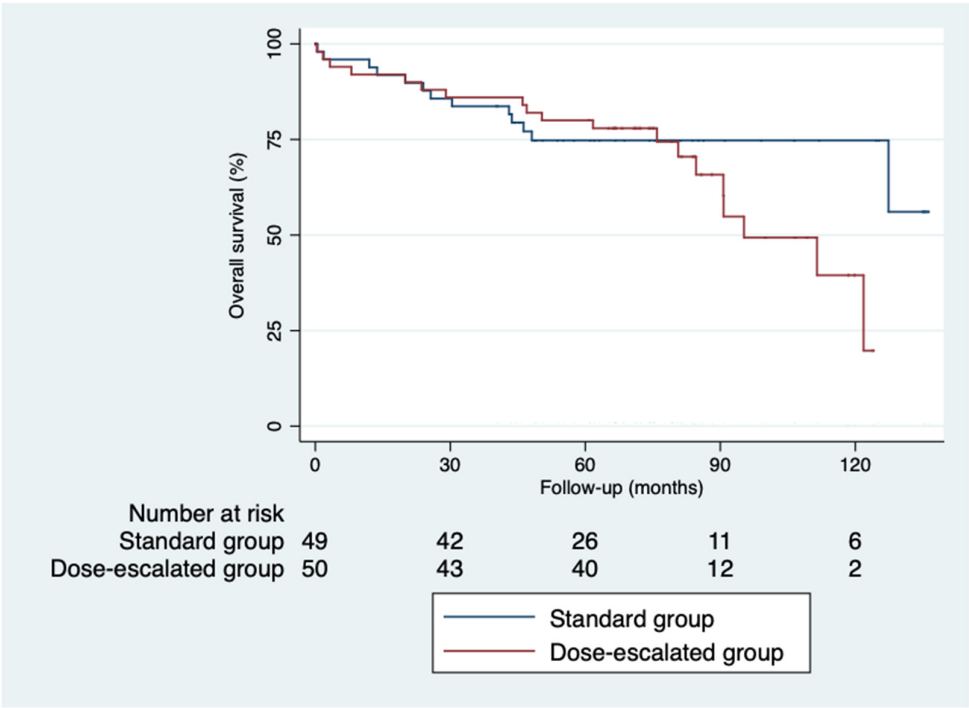


Figure 3. Kaplan-Meier curves for overall survival.

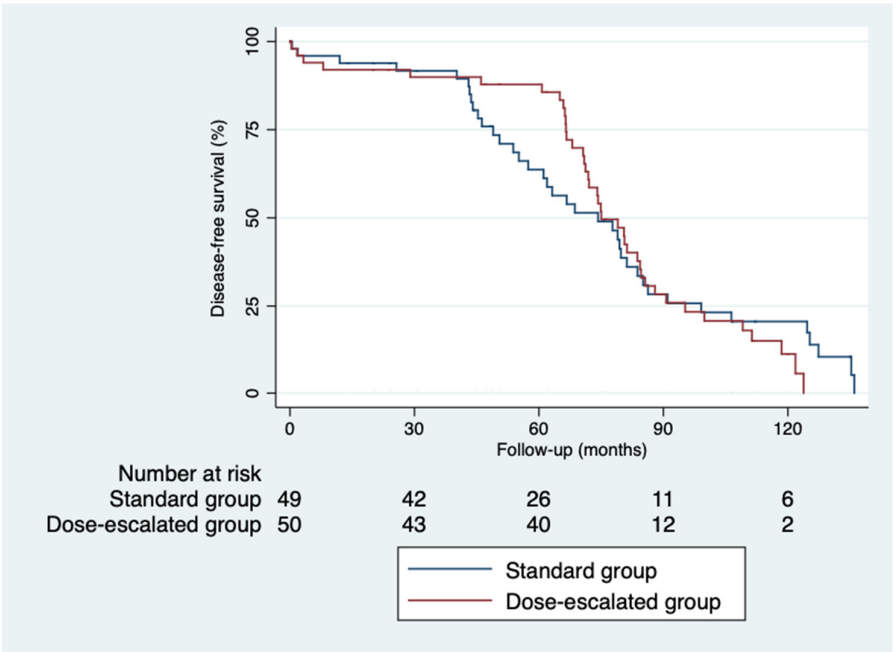


Figure 4. Kaplan-Meier curves for disease-free survival.

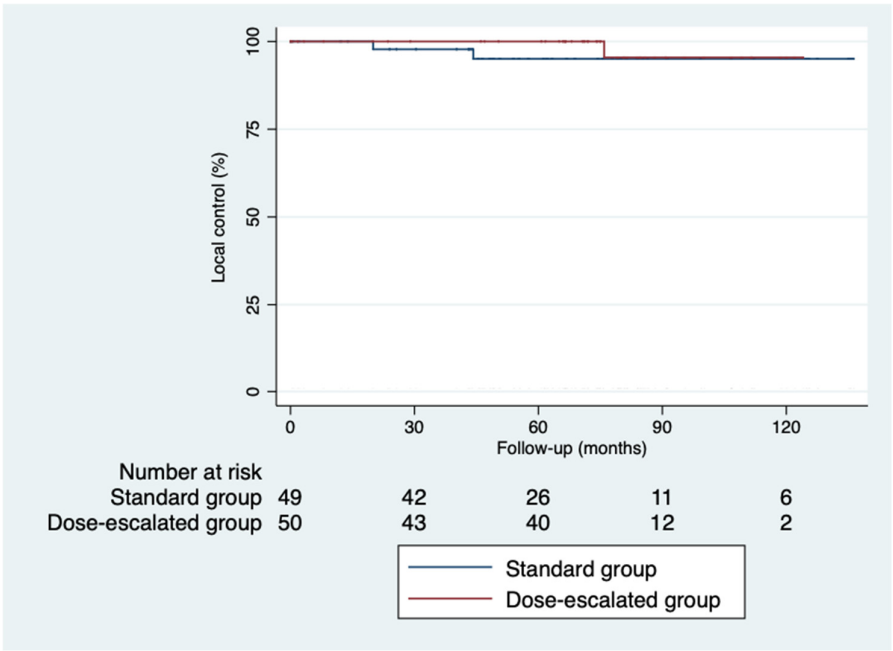


Figure 5. Kaplan-Meier curves for local control.

4. Discussion

Intensifying the neoadjuvant treatment by increasing the radiotherapy dose in patients diagnosed with locally advanced rectal cancer (LARC) achieved ypCR rates of 25% in our series, similar to those reported in the literature in dose escalation studies [36,37]. These results are higher than expected with the administration of the standard radiotherapy regimen [18–20], without a relevant increase in postoperative complications or toxicity.

Preoperative treatment of locally advanced rectal cancer with chemoradiotherapy was established as the standard to reduce tumor volume and achieve R0 surgeries, as well as lower rates of complications and toxicity compared to administering radiotherapy postoperatively [21]. Since then, new neoadjuvant treatment regimens have been sought to increase disease-free survival and overall survival. The ypCR is considered an independent factor for increasing local control (LC) and disease-free survival (DFS) [38–41]. Our treatment regimen is based on the Xelac arm of the phase III Interact Trial [42], which establishes concurrent boost with capecitabine as the reference regimen for neoadjuvant therapy. Our primary objective was to compare ypCR in a group of patients treated with integrated dose escalation of the tumor versus standard doses of radiotherapy. Unlike the Interact Trial, where the boost was administered twice a week for 5 weeks, in our case, it was administered from the beginning at a dose of 2.16 Gy/day reaching 54 Gy instead of the 55 Gy of the Interact Trial, although this represents an equivalent biological dose (BED). The goal of increasing the number of ypCR with dose escalation versus the standard regimen was achieved (25% vs 10.64%; $p = 0.07$). Both short, and long-term toxicity were acceptable, considering our regimen safe.

To our knowledge, the first study that had evaluated the pathological response rate by increasing the RT dose in American patients to 52.5 Gy in conjunction with intravenous 5 FU was published in 2000 [43]. Subsequently, in 2006, the same group published long-term results for 54 patients, reporting the same RT dose, but concurrent with oral capecitabine, demonstrating a safety profile. They achieved an 18% ypCR rate and a 59% downstaging rate. The first meta-analysis published in 2014 gathered studies conducted to date with 3D irradiation technique using dose escalation via linear accelerator or, in some cases, high-dose-rate brachytherapy; none used IMRT technique. It concluded that increasing the dose to ≥ 60 Gy in LARC increases the ypCR rate with acceptable acute toxicity, although randomized controlled trials with larger patient samples are needed [36]. The second, more recent meta-analysis from 2021 includes studies using intensity-

modulated radiation therapy (IMRT) with accelerated boost (between 54-60 Gy) that were not included in previous studies. It concludes that a dose of ≥ 54 Gy is associated with high ypCR rates close to 25%, achieved with a dose boost of between 54 and 60 Gy with IMRT, all without increasing the risk of grade III acute toxicity. However, a clear dose-response relationship was not identified in the regression analysis. The optimal boost dose has not been determined, and data on late toxicity and long-term oncological outcomes are lacking in the literature [37]. Other studies using integrated boost with IMRT are those by Hernando-Requejo [44] and Jin-luan Li [45], reporting ypCR rates close to 31%. Except for these two studies, we do not know any others that report higher ypCR rates.

From the bivariate analyses, we found that the variable influencing the achievement of ypCR is clinical tumor size (cT). Patients with a favorable profile for better tumor regression are those with tumors not presenting deep invasion. A recently published retrospective study similar to ours by Qi Zhang [46] found that CEA and surgical interval >8 weeks are variables influencing higher pathological response rates. In our case, we did not obtain sufficient statistical significance due to the smaller sample size. However, we obtained a higher ypCR rate (25% in our series vs. 20.8% reported in Qi Zhang's study). Since the introduction of advanced techniques (IMRT) no more patients are treated with 3DRT planning in our institution and that explains the sample of this study. The p-value of 0.09 for suture failures in anastomoses is not negligible. Confounding factors such as the surgical team with practicing surgeons, the type of suture material used, or intraoperative complications that might explain this higher rate have not been considered. A review is planned in the near future with an IMRT dose-escalated boost using the same scheme that is reported in the present study.

5. Conclusions

In our study we found a trend towards a higher ypCR-rates with neoadjuvant 3DRT intensification compared to the standard scheme with no differences in terms of postoperative complications and acceptable early and late toxicity rates. Long-term follow-up shows no differences in disease-free and overall survival. Well-designed randomized and controlled trials are needed to obtain conclusive data.

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