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ORIGINAL ARTICLE

Neoadjuvant chemo-radiotherapy for cT3N0 rectal cancer: any benefit over upfront surgery? A propensity score-matched study

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Abstract

Purpose Benefits of neoadjuvant chemo-radiotherapy (CRT) are well known for locally advanced and/or node-positive rectal cancer, but the best timing for CRT has been less explored for cT3N0 patients. The aim of the present study was to compare the 5-year disease-free survival (DFS) probability between neoadjuvant CRT and upfront surgery in patients affected by cT3N0 rectal cancer.

Methods A retrospective review of 105 patients affected by cT3N0 rectal cancer, staged by pelvic magnetic resonance imaging and treated at the National Cancer Institute of Milan between 2011 and 2017, was performed: 42 (40.0%) were treated by neoadjuvant CRT and 63 (60.0%) by upfront surgery. Propensity score matching was performed to avoid selection bias, and Cox multivariate regression was used to analyze outcomes.

Results The 5-year DFS probability was 87.5% in neoadjuvant CRT patients vs. 90.0% in upfront surgery cases (Log-rank $p = 0.76$). The 5-year loco-regional recurrence-free survival probability was respectively 96.8% vs. 96.3% (Log-rank $p = 0.954$). On multivariate analysis, neoadjuvant CRT had no impact on DFS when compared to upfront surgery (adjusted HR 0.71, 95%CI 0.18–2.70, $p = 0.613$), but 61.9% of upfront surgery cases were treated by adjuvant chemo-radiation (adjusted HR 0.41, 95%CI 0.11–1.57, $p = 0.196$). The only independent predictor of improved DFS was age at diagnosis (adjusted HR 0.95, $p = 0.017$).

Conclusion CRT should be considered for cT3N0 patients, but its timing (neoadjuvant vs. adjuvant) seems not to affect the disease-free survival in the present cohort of patients.

Keywords Rectal cancer · T3N0 · Neoadjuvant chemo-radiation therapy · Surgery · Adjuvant radiotherapy

Introduction

Benefits of preoperative chemo-radiotherapy (CRT) for rectal cancer are well known in terms of down-staging up to pathological complete response, increasing rates of sphincter-saving surgery and significant reduction in local recurrences [1, 2]. Neoadjuvant CRT should be considered mandatory for all T3-T4 and/or node-positive patients, or whenever the anal sphincter is involved but a sphincter-saving surgery could be potentially carried out in case of downsizing [3]. Also rectal cancer patients staged as T3N0 require CRT to improve local control. However, whether clinically staged T3N0 patients should undergo neoadjuvant CRT in any case, included early cT3 patients, still has not been fully elucidated [3–8]. Accordingly, current guidelines accept both upfront surgery and neoadjuvant CRT as possible therapeutic options for cT3N0 patients, provided that the mesorectal margin is not threatened [3]. Another major concern to be considered is clinical upstaging of rectal cancer on imaging before decision-making. Indeed, pelvic magnetic resonance imaging (MRI) and rectal ultrasound might upstage rectal cancer in up to 15–40% of cases, potentially leading to the unnecessary administration of neoadjuvant CRT in patients in whom

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adjuvant CRT would be normally spared [9, 10]. A correct staging may be particularly challenging in case of T2/early T3 rectal cancers, since distinguishing mesorectal stranding from initial extramural spiculation is sometimes difficult [11]. An accurate selection of cT3N0 patients requiring neoadjuvant CRT is mandatory, because CRT is not free from complications, such as increased risk of anastomotic leakage, bowel obstruction, lower anterior resection syndrome and perineal wound complications in case of abdominoperineal resection [5, 12, 13]. On the other hand, excluding some other cT3N0 patients from neoadjuvant CRT could deprive them of a potential benefit in long-term local control. The aim of the present study was to compare the 5-year disease-free survival (DFS) probability, the loco-regional recurrence (LRR) and the distant metastases (DM) rates between neoadjuvant CRT and upfront surgery, in patients affected by cT3N0 rectal cancer.

Material and methods

Study population

A retrospective review on all patients affected by rectal cancer and treated at the Colorectal Surgery Unit of the National Cancer Institute of Milan (Italy), between January 2011 and December 2017, was performed. This study was authorized by the Institutional Review Board ("SEBASTIAN" project, protocol number 149/2019), and the informed consent to collect clinical data was obtained for each patient according to the standard institutional practice. Clinical data were acquired and stored in a dedicated database following the current European General Data Protection Regulation. Inclusion criteria were: preoperative diagnosis of rectal cancer proven on endoscopic biopsy, cT3N0 staging assessed on imaging, with extraperitoneal location and no evidence of synchronous distant metastases. Ultralow rectal cancers with evidence of anal sphincters infiltration were excluded from the study, since these patients were mandatorily treated by neoadjuvant chemo-radiation according to guidelines, aiming to improve the probability of a sphincter-saving surgery. All patients underwent pelvic MRI, which was reviewed by a dedicated radiologist with expertise in rectal cancer staging. cT3 stage was defined as the evidence of infiltration of the mesorectal tissue with spiculations into perirectal fat, and it was distinguished according to mesorectal extension depth in T3a (< 1 mm), T3b (1–5 mm), T3c (5–15 mm) and T3d (> 15 mm). cN0 stage was defined as the absence of mesorectal lymph nodes with a size > 5 mm and/or with irregular borders and inhomogeneous signal. In case of unclear T and/or N stage on MRI, rectal ultrasound was performed to define clinical staging.

Study design and endpoints

Patients were divided in two groups: those who were treated by neoadjuvant CRT and those who underwent upfront surgery as the first treatment. Due to the non-random design of the study, a 1:1 propensity score-based matching was performed between the two patients' cohorts. Matching of patients was performed including variables with a potential confounding effect, such as age at diagnosis, distance of cancer from the anal verge, type of surgery (anterior rectal resection vs. abdominoperineal resection, pT stage and chemotherapy regimen (capecitabine vs. oxaliplatin-based). The main endpoints of the study were: (1) DFS probabilities and (2) the LRR-free and DM-free survival probabilities in patients treated with neoadjuvant CRT vs. patients treated by upfront surgery. LRR was defined as the occurrence of pelvic mass or regional lymphadenopathy on CT scan or MRI and/or intraluminal anastomotic lesion on endoscopy, proven on biopsy or with imaging features highly suggestive of malignancy. DM was defined as the occurrence of distant lesions on imaging (CT scan and/or positron emission tomography). Then, a multivariate survival analysis was carried out to evaluate the impact of neoadjuvant CRT vs. upfront surgery, accounting for all the other variables possibly related to LRR and DM, including age at diagnosis, type of surgery, pT stage, pN stage, margins status, adjuvant radiotherapy and adjuvant chemotherapy. Secondary endpoints were to assess the postoperative hospitalization stay, the complications rates and re-interventions between the two groups of patients. Finally, patients were stratified into low-intermediate and high-risk groups according to the last European Society of Medical Oncology practice guidelines, based on mesorectal infiltration depth evaluated on MRI and distance from the anal verge at endoscopy [6]. Briefly, patients were considered at low or intermediate risk in case of cT3a-b low, middle or high rectal cancer provided that circumferential mesorectal fascia and levators were clear; at high risk in case of >cT3b and/or very low localization with threatened levators. Event rate was compared in each risk group for each type of treatment.

Multidisciplinary treatment of rectal cancer

All patients were evaluated at the weekly multidisciplinary meeting of the Colorectal Surgery Unit after completion of clinical staging by pelvic MRI. Based on clinical features, mainly the distance from the anal verge, age at diagnosis and the possible presence of comorbidities, patients were proposed for neoadjuvant CRT or upfront surgery. In case of neoadjuvant CRT, patients received 825 mg/m^2 BID of capecitabine and concurrent administration of radiotherapy (total dose: 54 Gy delivered in 25–27 fractions) targeted to the mesorectum and pre-sacral space. Then, surgery was planned about 8 weeks after completion of neoadjuvant treatment. In

case of upfront surgery, this was planned within 30 days from the diagnosis. In all cases, surgery was performed with an open approach. Briefly, anterior rectal resection was carried out with nerve-sparing total mesorectal excision. A low ligation of the inferior mesenteric artery was preferred, and a stapled colo-rectal anastomosis by trans-anal circular stapler or manual colo-anal anastomosis was fashioned as appropriate depending on the distance from the anal verge. In case of low or ultralow anastomosis, a loop colostomy was also fashioned. In case of ultralow rectal cancer, an intraoperative trans-anal biopsy at the distal margin of the lesion was performed for immediate pathological evaluation and, if positive, abdominoperineal resection was carried out. If final pathology revealed a pT2N+ or a pT3-T4, any N cancer, adjuvant chemotherapy with or without radiotherapy was planned. In case of residual disease after neoadjuvant CRT, completion adjuvant chemotherapy could be proposed with an oxaliplatin-based regimen. Follow up was performed by thoracic and abdominal computed tomography, colonoscopy and CEA every 6 months for 5 years. Pelvic MRI and/or positron emission tomography could be added if LRR or DM were suspected.

Statistical analysis

Differences between neoadjuvant CRT and upfront surgery patients after propensity score matching were assessed to verify the heterogeneity of the study population. Variables were reported as mean ± standard deviations or as absolute numbers and percentages. Categorical variables were compared using a χ^2 test or Fisher exact test, while continuous variables were compared using a Student's *T* test or non-parametric Wilcoxon test as appropriate. The two treatment approaches were compared by a Cox proportional hazards regression model, including variables significantly associated with the outcomes to avoid any bias. The DFS probabilities were estimated by the Kaplan-Meier method. Statistical significance was set at $p < 0.05$ (two-tailed). Data analysis was performed using SAS software (v. 9.4, SAS Institute Inc., Cary, NC, USA).

Results

Distribution of baseline characteristics between groups before and after propensity score matching

A total of 105 cT3N0 rectal cancer patients were included in the study population: 42 patients (40.0%) were treated by neoadjuvant CRT, while the remaining 63 patients (60.0%) were treated by upfront surgery. Distribution of baseline characteristics is reported in Table 1. After 1:1 matching based on propensity score, a total of 84 patients were included for subsequent analyses. Mean distance of the lesion from the anal verge was 3.2 in the neoadjuvant CRT group vs. 5.2 cm in the upfront surgery group ($p = 0.001$). A sphincter-saving surgery was performed respectively in 37 (88.1%) vs. 41 (97.6%) cases ($p = 0.202$). On final histopathology a pT3 cancer was found in 13 (31.1%) neoadjuvant CRT patients vs. 37 (88.1%) upfront surgery patients ($p < 0.001$). Pathological complete response (pCR) was achieved in 12 cases (28.6%). In 4 (9.5%) upfront surgery patients a pT2 rectal cancer was detected, while 1 case (2.4%) was upstaged to pT4. Adjuvant chemotherapy was indicated in 18 (42.9%) neoadjuvant CRT patients and in 39 (92.9%) upfront surgery patients ($p < 0.001$); in the latter group, 3 patients (7.1%) avoided chemotherapy at all. All the other variables were similarly distributed between the two groups after propensity score matching, as reported in Table 1.

Post-operative outcomes

In all cases rectal resection was performed by open approach. No differences were observed in overall complications rate, occurring in 12 (28.6%) neoadjuvant CRT patients vs. 8 (19.0%) upfront surgery patients ($p = 0.443$). According to Clavien-Dindo classification, among neoadjuvant CRT patients complications were classified as grade I in 4 (33.3%) cases, II in 1 (8.3%) case, IIIa in 2 (16.7%) cases and IIIb in 5 (41.7%) cases. Among upfront surgery patients the same complications occurred respectively in 2 (25.0%), 1 (12.5%), 1 (12.5%) and 4 (50.0%) cases. In particular, anastomotic leakage occurred in 3 (7.1%) neoadjuvant CRT patients vs. 4 (9.5%) upfront surgery patients ($p = 1.000$), and a re-intervention was necessary respectively in 5 (11.9%) and 1 (2.4%) cases ($p = 0.202$). Post-operative outcomes are reported in Table 2.

Oncologic outcomes after neoadjuvant chemo-radiotherapy vs. upfront surgery

Median follow up was 41.5 months (interquartile range: 33–58) for neoadjuvant CRT patients vs. 38.0 months (interquartile range: 26–52) for upfront surgery cases. A total of 41 patients (48.8%) reached the 5-year follow up. A LRR occurred in 6 (14.3%) neoadjuvant CRT patients vs. 5 (11.9%) upfront surgery cases ($p = 1.000$), while DM occurred respectively in 7 (16.7%) and 5 (11.9%) patients ($p = 0.757$). Cancer-related death occurred in 3 cases (7.1%) of neoadjuvant CRT group ($p = 0.387$, Table 3).

Impact of neoadjuvant chemo-radiotherapy vs. upfront surgery upon risk stratification

On a total of 46 low-intermediate risk patients, 29 (63.0%) were treated by upfront surgery and 17 (37.0%) by neoadjuvant CRT; the same approaches were used respectively in 13 (34.2%) and 25 (65.8%) high-risk patients. Any first event occurred in 5 (17.2%) low-intermediate risk patients treated

Table 1 Distribution of baseline characteristics between neoadjuvant CRT and upfront surgery patients before and after propensity score matching

	Baseline			After propensity score matching		
	Neoadjuvant CRT ($n = 42$)	Upfront surgery ($n = 63$)	p value	Neoadjuvant CRT ($n = 42$)	Upfront surgery ($n = 42$)	p value
Age at diagnosis (years)	62.8 (± 11.8)	65.1 (± 12.1)	0.338	62.8 (± 11.8)	64.1 (± 12.5)	0.625
Gender						
Male	27 (64.3%)	37 (58.7%)	0.684	27 (64.3%)	23 (54.8%)	0.505
Female	15 (35.7%)	26 (41.3%)		15 (35.7%)	19 (45.2%)	
Mesorectal extension depth on MRI						
T3a	11 (26.2%)	22 (34.9%)	0.546	11 (26.2%)	13 (30.9%)	0.739
T3b	9 (21.4%)	17 (27.0%)		9 (21.4%)	12 (28.6%)	
T3c	16 (38.1%)	18 (28.6%)		16 (38.1%)	12 (28.6%)	
T3d	6 (14.3%)	6 (9.5%)		6 (14.3%)	5 (11.9%)	
Preoperative CEA (ng/mL)	2.7 (± 3.0)	5.5 (± 8.8)	0.05	2.7 (± 3.0)	5.1 (± 7.6)	0.061
Preoperative CA 19.9 (U/mL)	13.2 (± 12.6)	17.3 (± 32.2)	0.434	13.2 (± 12.6)	20.2 (± 38.7)	0.268
Distance from the anal verge (cm)	3.2 (± 2.5)	6.0 (± 3.1)	< 0.001	3.2 (± 2.5)	5.2 (± 2.7)	0.001
Surgery						
Anterior rectal resection	37 (88.1%)	62 (98.4%)	0.037	37 (88.1%)	41 (97.6%)	0.202
Abdominoperineal resection	5 (11.9%)	1 (1.6%)		5 (11.9%)	1 (2.4%)	
Colostomy						
Yes	40 (95.2%)	54 (85.7%)	0.193	40 (95.2%)	38 (90.5%)	0.676
No	2 (4.8%)	9 (14.3%)		2 (4.8%)	4 (9.5%)	
pT stage						
pT0	12 (28.6%)	0 (0.0%)	< 0.001	12 (28.6%)	0 (0.0%)	< 0.001
pT1	2 (4.8%)	0 (0.0%)		2 (4.8%)	0 (0.0%)	
pT2	15 (35.7%)	8 (12.7%)		15 (35.7%)	4 (9.5%)	
pT3	13 (31.0%)	54 (85.7%)		13 (31.0%)	37 (88.1%)	
pT4	0 (0.0%)	1 (1.6%)		0 (0.0%)	1 (2.4%)	
pN stage						
pN0	34 (81.0%)	51 (81.0%)	1.000	34 (81.0%)	33 (78.6%)	1.000
pN+	8 (19.0%)	12 (19.0%)		8 (19.1%)	9 (21.5%)	
Retrieved nodes (mean)	13.4 (± 5.6)	19.4 (± 8.0)	< 0.001	13.4 (± 5.6)	18.8 (± 8.4)	0.001
Grading						
G2	35 (83.3%)	50 (79.4%)	0.8	35 (83.3%)	31 (73.8%)	0.426
G3	7 (16.7%)	13 (20.6%)		7 (16.7%)	11 (26.2%)	
Margins status						
R0	36 (85.7%)	54 (85.7%)	1.000	36 (85.7%)	35 (83.3%)	1.000
R1	6 (14.3%)	9 (14.3%)		6 (14.3%)	7 (16.7%)	
Circumferential resection margin						
Positive	2 (4.8%)	2 (3.2%)	1.000	2 (4.8%)	1 (2.4%)	1.000
Negative	40 (95.2%)	61 (96.8%)		40 (95.2%)	41 (97.6%)	
Adjuvant chemo-radiotherapy						
Yes	-	45 (71.4%)	-	-	26 (61.9%)	-
No	-	18 (28.6%)		-	16 (38.1%)	
Adjuvant chemotherapy						
Yes	18 (42.9%)	49 (77.8%)	< 0.001	18 (42.9%)	39 (92.9%)	< 0.001
No	24 (57.1%)	14 (22.2%)		24 (57.1%)	3 (7.1%)	
Chemotherapy regimen						
Capecitabine	30 (71.4%)	37 (58.8%)	0.014	30 (71.4%)	27 (64.3%)	0.564
Oxaliplatin-based	12 (28.6%)	12 (19.0%)		12 (28.6%)	12 (28.6%)	
None	0 (0.0%)	14 (22.2%)		0 (0.0%)	3 (7.1%)	

by upfront surgery, 4 (30.8%) high-risk patients treated by upfront surgery, 4 (23.5%) low-intermediate risk patients treated by neoadjuvant CRT, and 6 (24.0%) high-risk patients treated by neoadjuvant CRT ($p = 0.799$, see Fig. 1).

Survival probabilities after propensity score matching

Only patients included after propensity score matching were considered for survival analysis. The 1-year, 3-year and 5-year DFS probabilities were respectively 97.2%, 96.4% and 87.5% among neoadjuvant CRT patients and 97.1%, 96.2% and 90.0% among upfront surgery patients (overall Log-rank $p = 0.76$, see Fig. 2). The 1-year, 3-year and 5-year LRR-free survival probabilities were 97.4%, 96.8%, 96.8% for neoadjuvant CRT group vs. 94.9%, 96.3% and 96.3% for surgery group (Log-rank $p = 0.954$, Fig. 3a). The 1-year, 3-year and 5-year DM-free survival probabilities were 97.2%, 96.9%,

Table 2 Post-operative complications

	Neoadjuvant chemo-radiotherapy ($n = 42$)	Upfront surgery ($n = 42$)	p value
Post-operative complications			
Yes	12 (28.6%)	8 (19.0%)	0.443
No	30 (71.4%)	34 (81.0%)	
Anastomotic leakage			
Yes	3 (7.1%)	4 (9.5%)	1.000
No	39 (92.9%)	38 (90.5%)	
Bleeding			
Yes	3 (7.1%)	1 (2.4%)	0.616
No	39 (92.9%)	41 (97.6%)	
Pre-sacral abscess/infection			
Yes	8 (19.0%)	3 (7.1%)	0.194
No	34 (81.0%)	39 (92.9%)	
Bowel obstruction			
Yes	1 (2.4%)	0 (0.0%)	1.000
No	41 (97.6%)	42 (100.0%)	
Re-intervention			
Yes	5 (11.9%)	1 (2.4%)	0.202
No	37 (88.1%)	41 (97.6%)	
Post-operative stay (days)	9.3 (± 3.6)	9.9 (± 3.7)	0.454

87.5% and 97.3%, 97.3%, 87.5% respectively in the two groups (Log-rank $p = 0.419$, Fig. 3b).

Multivariate survival analysis of neoadjuvant chemo-radiotherapy vs. upfront surgery

On univariate analysis, neoadjuvant CRT had no impact on DFS probability when compared to upfront surgery (HR 0.51, 95%CI 0.09–2.87, $p = 0.449$), while age at diagnosis (HR 0.95, 95%CI 0.89–1.00, $p = 0.066$) and adjuvant radiotherapy (HR 0.15, 95%CI 0.02–1.06, $p = 0.057$) showed an almost significant effect on DFS (Table 4, Supplementary Figure S1). After adjusting for confounding variables possibly related with DFS in the multivariate survival analysis, the use of neoadjuvant CRT over upfront surgery confirmed not to carry a significant benefit on DFS (adjusted HR 0.71, 95%CI 0.18–2.70, $p = 0.613$). The only independent predictor of improved DFS was age at diagnosis (adjusted HR 0.95, 95%CI 0.92–0.99, $p = 0.017$). The multivariate survival analysis has been reported in Table 4.

Discussion

The standard of care for locally advanced and/or node-positive rectal cancer is neoadjuvant CRT, since a significant benefit over adjuvant CRT in terms of local control and DFS has been demonstrated in previous randomized clinical trials [14, 15].

Table 3 Crude rates of loco-regional recurrence, distant metastases and cancer-related death

	Neoadjuvant chemo-radiotherapy ($n = 42$)	Upfront surgery ($n = 42$)	p value
Loco-regional recurrence			
Yes	6 (14.3%)	5 (11.9%)	1.000
No	36 (85.7%)	37 (88.1%)	
Distant Metastases			
Yes	7 (16.7%)	5 (11.9%)	0.757
No	35 (83.3%)	37 (88.1%)	
Cancer-related death			
Yes	3 (7.1%)	0 (0.0%)	0.241
No	39 (92.9%)	42 (100.0%)	

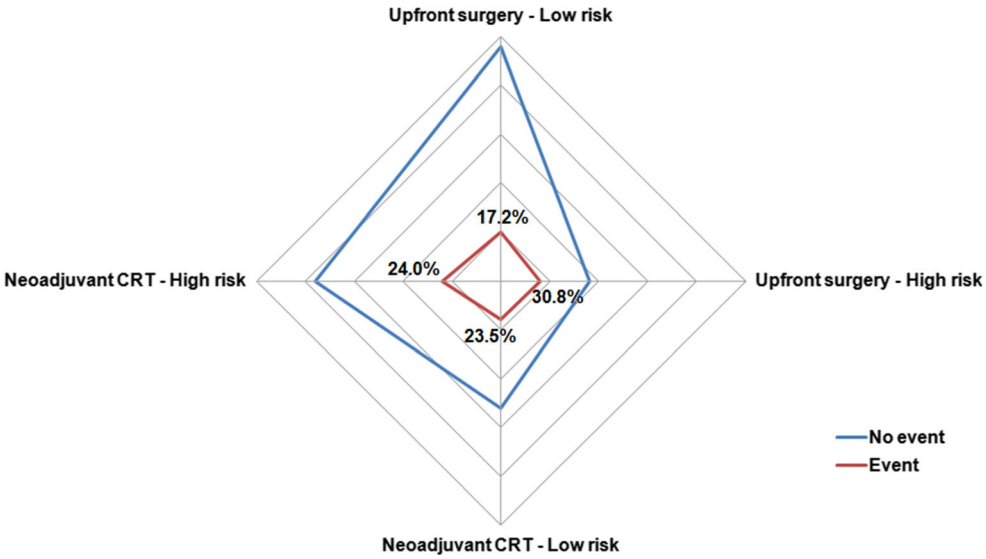

Fig. 1 Distribution of events among low-intermediate and high-risk patients treated by surgery-first vs. neoadjuvant chemo-radiotherapy

However, the benefit of neoadjuvant CRT on DFS for all cT3N0 patients, in the era of precision medicine and proper patients' selection, needs to be fully elucidated. The present study specifically assessed oncologic outcomes between neoadjuvant CRT vs. upfront surgery in a population of cT3N0 patients. After propensity score-based matching, no difference was found between neoadjuvant CRT vs. upfront surgery on 5-year DFS probability, being respectively 87.5% vs. 90.0% (Log-rank $p = 0.76$). No clinical benefit of neoadjuvant CRT over upfront surgery was observed also for 5-year LRR-free (Log-rank $p = 0.954$) and DM-free (Log-rank $p = 0.419$) survival probabilities. Furthermore, at multivariate survival analysis neoadjuvant CRT resulted not to be a significant predictor of DFS (HR 0.71, $p = 0.613$). Adjuvant CRT showed an almost significant correlation with improved DFS on univariate (HR 0.15, $p = 0.057$) but not multivariate analysis (HR 0.41, $p = 0.196$).

Some explanations might be hypothesized to explain the similar outcomes between neoadjuvant CRT and upfront surgery in terms of DFS. First, 61.9% of upfront surgery patients underwent adjuvant CRT, therefore the great majority of patients anyway received chemo-radiation. It could be supposed that, in selected low-risk T3N0 patients, timing of CRT (neoadjuvant vs. adjuvant) may not affect the DFS, provided that adequate total mesorectal excision and chemo-radiation are offered. Secondly, comparison was performed between patients with unknown preoperative pathological staging undergoing neoadjuvant CRT and patients treated after postoperative pathological staging. Therefore, considering possible inaccuracies of imaging, a subset of T2 patients preoperatively upstaged as cT3 could undergo CRT, thus biasing to the expected benefit of neoadjuvant CRT on DFS in true T3N0 patients. Interestingly, 9.5% of upfront surgery patients were

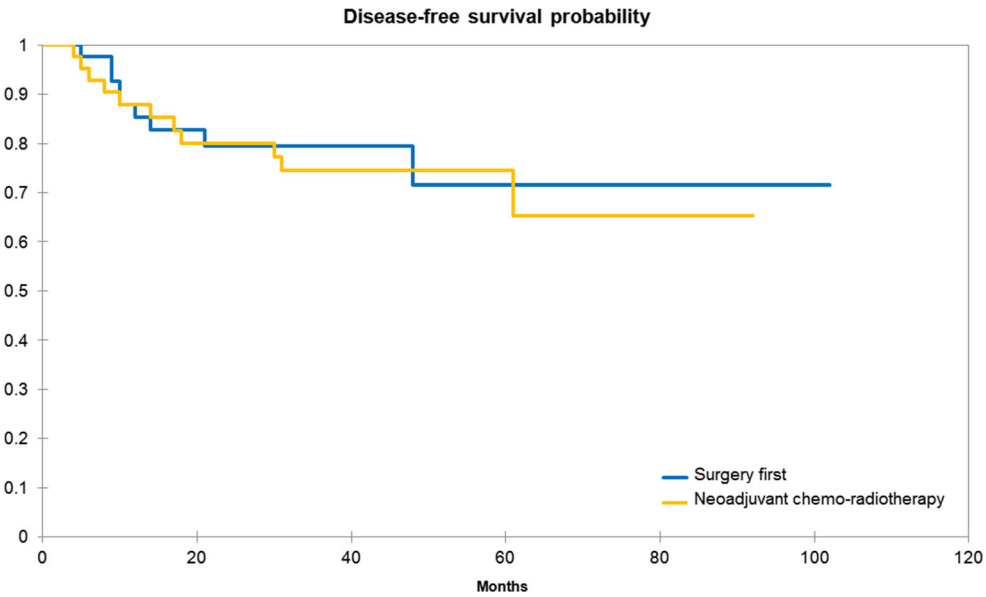

Fig. 2 Disease-free survival probabilities in patients treated by surgery-first vs. neoadjuvant chemo-radiotherapy

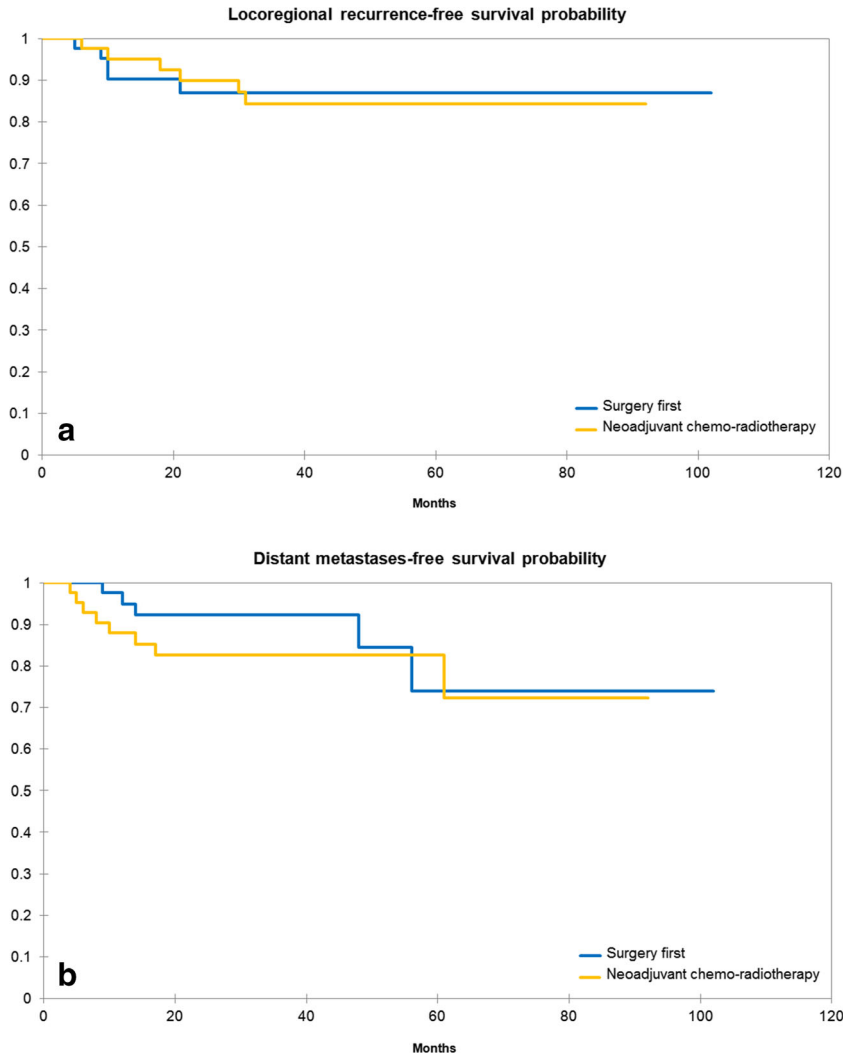

Fig. 3 Loco-regional recurrence-free (**a**) and distant metastases-free (**b**) survival probabilities in patients treated by surgery-first vs. neoadjuvant chemo-radiotherapy

down-staged to pT2N0, as a result of preoperative pelvic MRI upstaging. Accurately distinguishing cT2 from cT3 lesions is not a secondary concern, because in the former case neoadjuvant CRT is not indicated, and surgery alone is the elective treatment. Furthermore, if pT2N0 rectal cancer is confirmed the patient will definitively avoid CRT.

Despite 90.5% of upfront surgery patients were affected by pT3-T4 rectal cancer, only 61.9% received adjuvant CRT. Therefore, 12 pT3-T4 patients have not received radiotherapy: in 8 cases it was due to lesion location in the higher rectum (anyway below the peritoneal reflection), thus after multidisciplinary discussion radiotherapy was not proposed. In the remaining 4 cases radiotherapy was indicated but not delivered due to the occurrence of anastomotic leakage and subsequent management of septic complications. These data remark that a major benefit of neoadjuvant CRT is that delivery of chemo-radiation is not prevented by possible post-operative complications.

Several landmark clinical trials demonstrated a significant improvement in local control and DFS thanks to neoadjuvant CRT for locally advanced rectal cancer [1, 14, 16, 17]. The role of neoadjuvant CRT has gained such a wide consensus, that incorporating chemo-radiation and systemic chemotherapy in the preoperative setting (the so-called total neoadjuvant therapy) has been recently explored, promising to increase organ-preserving strategies [18]. The benefit of preoperative treatment was specifically assessed for T3N0 patients in the German Rectal Cancer Study Group trial, which reported neoadjuvant CRT to be equivalent with adjuvant radiotherapy, and in the National Surgical Adjuvant Breast and bowel Project (NSABP) trial, which established that neoadjuvant CRT is related to significantly improved survival [1, 15]. A recent Surveillance, Epidemiology and End Results (SEER)-based analysis specifically focused on T3N0 rectal cancer showed a decreased risk of cancer-specific death with adjuvant radiotherapy [19]. According to our findings and the published evidences, the take-home message might be that CRT should be considered mandatory for cT3N0 patients, but its timing (neoadjuvant vs. adjuvant) seems not to affect the DFS in selected cases.

Table 4 Univariate and multivariate survival analysis

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p* value	HR	95%CI	*p* value
Age at diagnosis	0.95	0.89–1.00	0.066	0.95	0.92–0.99	0.017
Preoperative CEA	0.98	0.84–1.15	0.822			
Preoperative CA 19.9	1.02	0.99–1.05	0.241			
Distance from the anal verge	1.10	0.84–1.44	0.476			
Mesorectal extension depth on MRI:						
T3c-d vs. T3a-b	1.11	0.57–2.18	0.762			
Treatment: Neoadjuvant chemo-radiotherapy vs. upfront surgery	0.51	0.09–2.87	0.449	0.71	0.18–2.70	0.613
Type of surgery: abdominoperineal resection vs. anterior rectal resection	3.51	0.36–34.31	0.280	2.13	0.47–9.76	0.332
pT stage:						
pT2–4 vs. pT0–1	1.37	0.22–8.46	0.732	0.89	0.53–1.49	0.657
pN stage: pN+ vs. pN0	2.40	0.30–19.44	0.412	1.83	0.55–6.02	0.325
Retrieved nodes	0.99	0.91–1.08	0.878			
Grading: G3 vs. G2	0.69	0.13–3.70	0.663			
Distal margin	0.97	0.91–1.04	0.455			
Margins status: R0 vs. R1	0.74	0.09–6.32	0.787	1.20	0.34–4.25	0.775
Adjuvant chemo-radiotherapy: Yes vs. no	0.15	0.02–1.06	0.057	0.41	0.11–1.57	0.196
Adjuvant chemotherapy: Yes vs. no	2.22	0.37–13.46	0.385	1.81	0.52–6.28	0.352
Chemotherapy regimen: Capecitabine vs. oxaliplatin-based	1.12	0.18–6.96	0.903			

Another point to be considered is that, despite inclusion of patients preoperatively staged as node-negative, 19.1% of patients treated by neoadjuvant CRT and 21.5% of those treated by upfront surgery were affected by node-positive disease on final pathology. Supposing that patients treated by preoperative CRT should have been down-staged, as demonstrated by different T stages between groups, it might be hypothesized that probably a higher rate of misdiagnosed node-positive disease was included in this group. Therefore, the similar DFS observed between groups should be cautiously considered, taking into account this data.

A major concern in performing this kind of retrospective study is that the chosen therapeutic approach could have been influenced by several confounding factors, which could bias final results. In both groups cancer was mostly located in the lower rectum, but expectedly a wider distance from the anal verge was related to upfront surgery as the preferred approach (5.2 vs. 3.2 cm, $p = 0.001$). Importantly, rectal cancer location is considered a fundamental driver for clinical decision, because low and ultralow T3N0 tumors are preferentially treated by neoadjuvant CRT to maximize the probability of a sphincter-saving surgery, while cancers of the upper rectum are rarely irradiated if staged as cT3a-b on MRI [8]. Furthermore, also a different final pathological staging between groups, due to the effect of neoadjuvant CRT, could be a confounding factor. While 88.1% of upfront surgery patients confirmed to have a T3 lesion on final pathology, the same pathological staging was observed in 31.0% only of patients treated by neoadjuvant CRT ($p < 0.0001$), since in the majority of cases rectal cancer was down-staged, up to pathological complete response in 28.6% of cases. Notably, the only independent predictor of improved DFS was age at diagnosis (HR 0.95, $p = 0.017$). As previously suggested, older patients are less likely to receive neoadjuvant or adjuvant treatments due to the higher frequency of comorbidities [20].

Some study limitations need to be considered. First, this is a single-center retrospective study. Despite the use of propensity score matching and multivariate survival analysis, the risk of bias is minimized but not completely avoided, due to the retrospective design. Moreover, after propensity score matching the analyses were carried out in a relatively small sample size. Furthermore, it should be noted that all cases were performed by open approach. A relevant expertise in laparoscopic rectal surgery has been only recently acquired in our Institution, and after 2017 (therefore outside the study period) laparoscopic rectal resection has been increasingly performed. Currently no guideline considers mandatory the laparoscopic approach for rectal cancer surgery, and the majority of evidences confirmed no significant differences between the two approaches in terms of oncologic outcomes [21, 22]. Therefore, it is unlikely that the surgical approach could have been biased the analyses on the oncologic outcomes of the present study, also considering that open rectal surgery was performed in 100% of cases in both groups of patients. However, the inclusion of laparoscopic rectal surgery

cases would have strengthened the relevance of our findings in an updated setting, especially when analyzing post-operative complications and hospitalization.

Conclusions

Neoadjuvant CRT is the gold standard for locally advanced and/or node-positive rectal cancer, providing improved loco-regional control. Use of CRT should be considered also for cT3N0 patients, but its timing (neoadjuvant vs. adjuvant) seems not to affect the disease-free survival in the present cohort of patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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