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ORIGINAL ARTICLE

Effect of delaying surgery by more than 10 weeks after neoadjuvant therapy in rectal cancer: a single institution experience

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Abstract

The optimal timing of surgery after neoadjuvant chemoradiotherapy (CRT) in locally advanced rectal cancer is still controversial. Aim of this study was to evaluate the effect of increasing time interval between the end of CRT and surgery on pathological outcomes. This is a retrospective analysis on 114 patients treated with long-course neoadjuvant RT with or without chemotherapy between January 2005 and September 2020. 43 patients underwent surgery within 10 weeks from the end of CRT (1st group), whereas 71 patients underwent total mesorectal excision with a time interval equal or greater than 10 weeks (2nd group). Primary endpoint was pCR (pathological complete response). Secondary endpoints were near pCR (ypT0–1 N0), tumor downstaging (ypT less than cT), nodal downstaging (ypN less than cN), and overall response comparing clinical with pathological TN stage. Overall, the pCR rate was 8.8%, whereas we observed no significantly difference in primary endpoint between the two groups. Considering near pCR, a trend toward significant difference in favor of 2nd group was seen ($p = 0.072$). Tumor and nodal downstaging rates were 39.5%, 41.9%, 59.2%, and 56.3% in the 1st and 2nd group, respectively, with a statistically significant difference for T category ($p = 0.042$). Overall response rates (TN stage) showed a trend toward significant difference in favor of patients of the ≥ 10 week group ($p = 0.059$). Our study suggests that a prolonged time interval between the end of CRT and surgery (≥ 10 weeks) increases pathological response rates.

Keywords Rectal cancer · Neoadjuvant chemoradiotherapy · Surgery · Time interval

Introduction

Preoperative radiotherapy (RT) or chemoradiotherapy (CRT) followed by a total mesorectal excision (TME) has become the standard of care for locally advanced rectal cancer (LARC) [1]. Neoadjuvant treatment is associated with improved tumor resectability by tumor downstaging or downsizing, increased local control rate, good toxicity profile, and highest compliance rate [2, 3]. Time interval between the end of CRT and surgery represents an important factor to obtain the maximum effect after neoadjuvant treatment and, consequently, to improve the pathological complete response rate (pCR) [4–6]. After the Lyon R90-01 study, published in 1999, the 6–8 week interval became the standard time for surgery after CRT [7]. Subsequently, several trials showed a correlation between a prolonged time interval and pathological complete response rate [8–12]. These observations led colorectal cancer community to delay surgery after the end of preoperative therapy. Nevertheless, the optimal time interval between CRT and TME still remains an unresolved question. In some studies, an interval beyond 10 weeks after neoadjuvant treatment resulted in an independent factor in improving pCR rate [13–15]. The purpose of this study was to analyze the effect of increase the timing of TME after preoperative RT or CRT (< 10 weeks or ≥ 10 weeks) on pathological response.

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Materials and methods

We retrospectively collected data on patients with diagnosis of LARC between January 2005 and September 2020 at our institution. Patients treated with long-course neoadjuvant RT with or without chemotherapy followed by surgery were included. We recorded demographic and pathological characteristics such as age, gender, clinical stage, type of treatment (RT or CRT), chemotherapy schedule, radiotherapy dose, and pathological response. All patients underwent elective surgery by the same surgical team, according to the principles of total mesorectal excision, or partial mesorectal excision when oncological feasible, and primarily laparoscopically. Patients with distant metastases, short-course radiotherapy, no surgery, or organ preservation approach as local excision and with incomplete informations were excluded.

At the beginning of our experience, surgery was performed 6–8 weeks after the end of neoadjuvant treatment. Later, based on the results obtained in patients underwent TME after a prolonged number of weeks due to anesthesiological problems or need for further investigations and in accordance with the emerging literature, we began to delay restaging after neoadjuvant therapy at 8 weeks after the end of treatment. Consequently, patients are more frequently underwent TME at 10 or more weeks after RT or CRT.

For this reason, in our study, patients were classified into two groups according to time interval, defined as the time between the end of the neoadjuvant therapy and the date of surgery. The 1st group included patients with a waiting interval of less than 10 weeks, and the 2nd group with a time interval equal or greater than 10 weeks.

The primary endpoint of the study was a pCR (pathological complete response), defined as the absence of tumor cells in the surgical specimen (ypT0N0). Secondary endpoints were near pCR, defined as ypT0–1 N0, tumor downstaging (ypT less than cT), and nodal downstaging (ypN less than cN). Moreover, we evaluated overall response comparing clinical with pathological stage. Consequently, "response" was defined as ypTN less than cTN, "stable disease" as ypTN = cTN and "progression" as ypTN greater than cTN. These rates were correlated with time interval between neoadjuvant treatment and surgery.

Statistical analysis

We calculated continuous variables as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages. Statistical differences in characteristics and outcome parameters between the two groups were tested using Chi-square and Student's *t* test. Univariate and multivariate logistic regression analyses were done to identify independent predictors of pCR. A p value ≤ 0.05 was considered significant. Statistical analysis was performed using SPSS software version 20 (IBM Corp., Armonk, New York, USA).

Results

Data of 114 patients with LARC who were treated using long-course CRT or only RT if chemotherapy not allowed for comorbidities and subsequent TME were analyzed. The 1st group included 43 patients who received surgery within 10 weeks, whereas in the 2nd group, 71 patients underwent TME with a time interval equal or greater than 10 weeks. The median days until surgery after neoadjuvant therapy completion were 70 (range 25–143). Patient, tumor, and treatment characteristics are reported in Table 1. There were no significant differences between the two groups in terms of age, sex, and clinical stage. Concurrent chemotherapy consisted in 5-FU and capecitabine in 28.2% and 71.8% in the 1st group, respectively, and in 6.5% and 93.5% in the 2nd group, respectively ($p = 0.009$). Radiotherapy dose resulted significantly different in the two groups, with a total dose > 50.4 Gy used only in 22.5% of the 2nd group ($p = 0.001$). A total of 105 intervention (92.1%) were performed laparoscopically.

Primary and secondary outcomes are shown in Table 2. The overall pCR rate was 8.8% (10 patients). The delayed surgery group showed a no significantly better pCR rate (4.7% versus 11.3%, $p = 0.226$). Considering pCR and near pCR, the highest response rate was found for patients with a time interval equal or greater than 10 weeks (22.5%), although this was not significantly different from the rate in the other group (9.3%, $p = 0.072$). Figures 1 and 2 show the rates of pCR and near pCR globally and according to time interval. Tumor and nodal downstaging were seen in 39.5%, 41.9%, 59.2%, and 56.3% in the 1st and 2nd group, respectively, with a statistically significant difference only for T category ($p = 0.042$). Response rates based on combined TN stage showed a trend toward significant difference in favor of patients of the ≥ 10 week group ($p = 0.059$). Figure 3 shows overall response comparing clinical with pathological TN stage.

At univariate and multivariate analysis, no significant correlations were found between pCR and evaluated factors (clinical T, clinical N, clinical stage, type of treatment, chemotherapy schedule, RT dose, and time interval).

Table 1 Patient, tumor, and treatment characteristics

	All ($n=114$)	<10 weeks ($n=43$)	≥ 10 weeks ($n=71$)	p value
Interval, days, median (range)	70 (25–143)	58 (25–67)	78 (70–143)	<0.001
Age, mean ± SD	64.48 ± 10.76	63.28 ± 9.90	65.21 ± 11.26	0.488
Sex				
Male	75 (65.8%)	28 (65.1%)	47 (66.2%)	0.906
Female	39 (34.2%)	15 (34.9%)	24 (33.8%)	
Clinical T stage				
T2	5 (4.4%)	0	5 (7%)	0.110
T3	100 (87.7%)	41 (95.3%)	59 (83.1%)	
T4	9 (7.9%)	2 (4.7%)	7 (9.9%)	
Clinical N stage				
N0	32 (28.1%)	13 (30.2%)	19 (26.8%)	0.876
N1	64 (56.1%)	24 (55.8%)	40 (56.3%)	
N2	18 (15.8%)	6 (14%)	12 (16.9%)	
Clinical stage				
II	32 (28.1%)	13 (30.2%)	19 (26.8%)	0.689
III	82 (71.9%)	30 (69.8%)	52 (73.2%)	
Treatment				
CRT	100 (87.7%)	39 (90.7%)	61 (85.9%)	0.451
Only RT	14 (12.3%)	4 (9.3%)	10 (14.1%)	
Chemotherapy schedule				
5-FU	15 (15%)	11 (28.2%)	4 (6.5%)	0.009
Capecitabine	85 (85%)	28 (71.8%)	57 (93.5%)	
RT dose				
≤ 50.4 Gy	98 (85.9%)	43 (100%)	55 (77.5%)	0.001
>50.4 Gy	16 (14.1%)	0	16 (22.5%)	

SD standard deviation, *CRT* chemoradiotherapy, *RT* radiotherapy, *5-FU* 5-fluorouracil

Table 2 Outcome parameters

	All ($n=114$)	<10 weeks ($n=43$)	≥ 10 weeks ($n=71$)	p value
pCR (ypT0N0)	10 (8.8%)	2 (4.7%)	8 (11.3%)	0.226
pCR and near pCR (ypT0–1N0)	20 (17.5%)	4 (9.3%)	16 (22.5%)	0.072
T downstaging (ypT < cT)	59 (51.8%)	17 (39.5%)	42 (59.2%)	0.042
N downstaging (ypN < cN)	58 (50.9%)	18 (41.9%)	40 (56.3%)	0.126
cTN versus ypTN				
Response (ypTN < cTN)	87 (76.3%)	29 (67.4%)	58 (81.7%)	0.059
Stable disease (ypTN = cTN)	22 (19.3%)	13 (30.2%)	9 (12.7%)	
Progression (ypTN > cTN)	5 (4.4%)	1 (2.3%)	4 (5.6%)	

pCR pathological complete response, *ypT/N* pathological tumor/node status after neoadjuvant therapy, *cT/N* clinical tumor/node category

Discussion and conclusion

In this retrospective study of a cohort of 114 patients with locally advanced rectal cancer undergoing neoadjuvant therapy, we found no statistically significant differences in the rate of pathological complete response, as well as in the rate of near pathological complete response (ypT0–1 N0), by prolonging the time interval between the end of RT or CRT and surgery. Nevertheless, the rate of pCR resulted higher in the group underwent surgery at ≥ 10 weeks after preoperative treatment (11.3%) compared to the patients with a waiting interval of less than 10 weeks (4.7%). Considering pCR and near pCR, there is a trend to a significant better oncological outcome

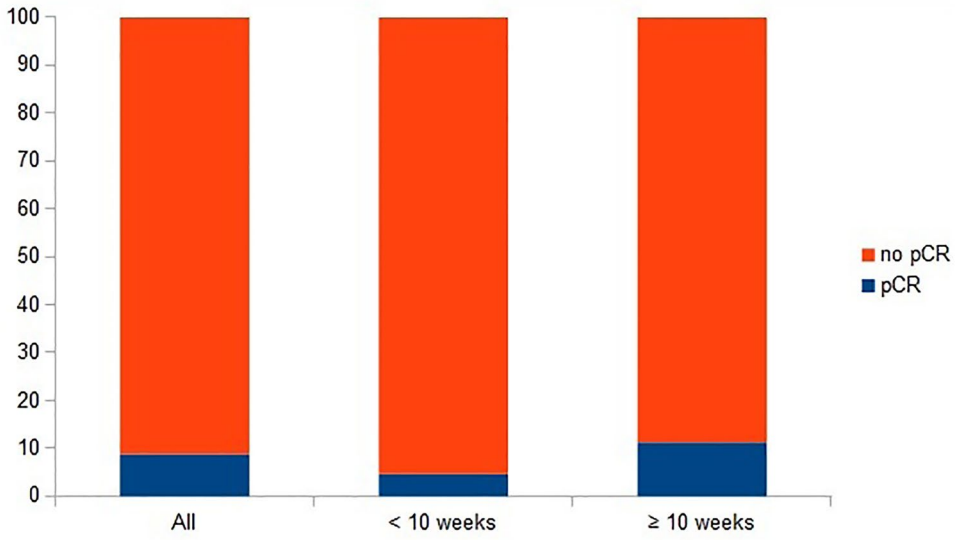

Fig. 1 Pathological complete response (pCR) rates, globally and according to time interval (< or ≥ 10 weeks)

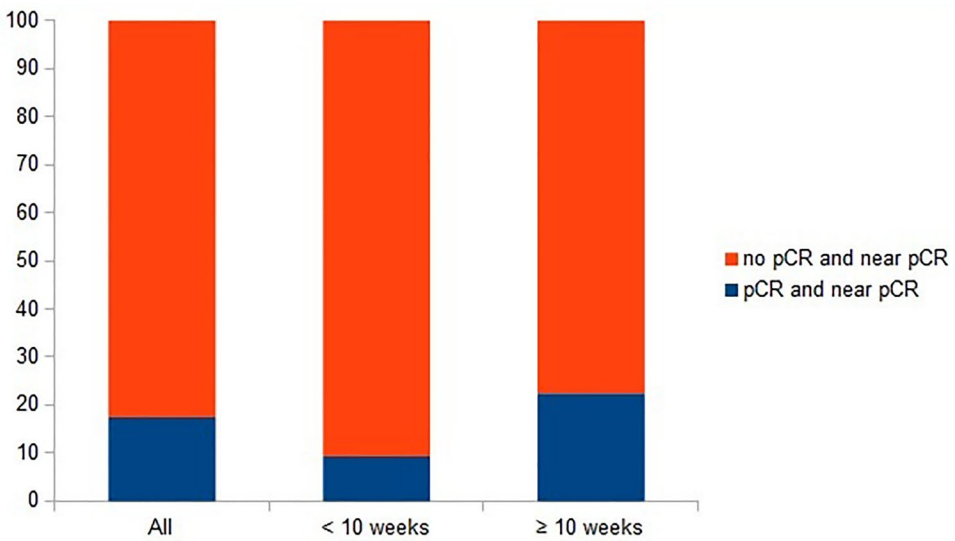

Fig. 2 Pathological complete (pCR) and near pathological complete response (near pCR) rates, globally and according to time interval (< or ≥ 10 weeks)

increasing the interval to surgery, with rates of 22.5% and 9.3% ($p = 0.072$) in the 2nd and the 1st group, respectively.

During the last decades, the growing interest about the importance of pCR in LARC led to different strategies to modulate neoadjuvant treatment by both increasing the RT dose and/or intensifying preoperative chemotherapy [16–18]. Lengthening of the time interval before surgery was identified as another important factor to obtain higher rates of downstaging and pCR [8, 11, 13, 19]. In the Lyon R90–01 trial, published in 1999, a total of 210 patients with rectal cancer were randomized between surgery after less than 2 weeks or at 6–8 weeks from the end of preoperative radiotherapy, showing a significantly higher proportion of patients with ypT0–1 disease with the longer interval. For this reason, 6–8 week interval became standard practice after CRT for LARC [7]. In the 2013, Sloothaak et al. reported that delaying surgery until the 15th or 16th week after the start of CRT (week 10 or 11 after the end of neoadjuvant treatment) results in the highest chance of a pCR [13]. In the population-based study of Rombouts et al., published in 2016, pCR rates in LARC patients resulted significantly higher after 9–10 weeks and 11–12 weeks of treatment interval compared with 7–8 weeks [20]. More recently, the retrospective analysis of the German StuDoQ | Rectal carcinoma registry divided patients into four subgroups according to the time interval between the end of preoperative CRT and the oncological resection (less than 6 weeks, 6–8 weeks, 8–10 weeks, and more than 10 weeks). Authors observed a trend for increased rates of pCR and pathological good response (ypT0–1 N0) for groups with a prolonged time interval [21]. In 2020, a Spanish study evaluated the effect and safety of increasing time interval between the

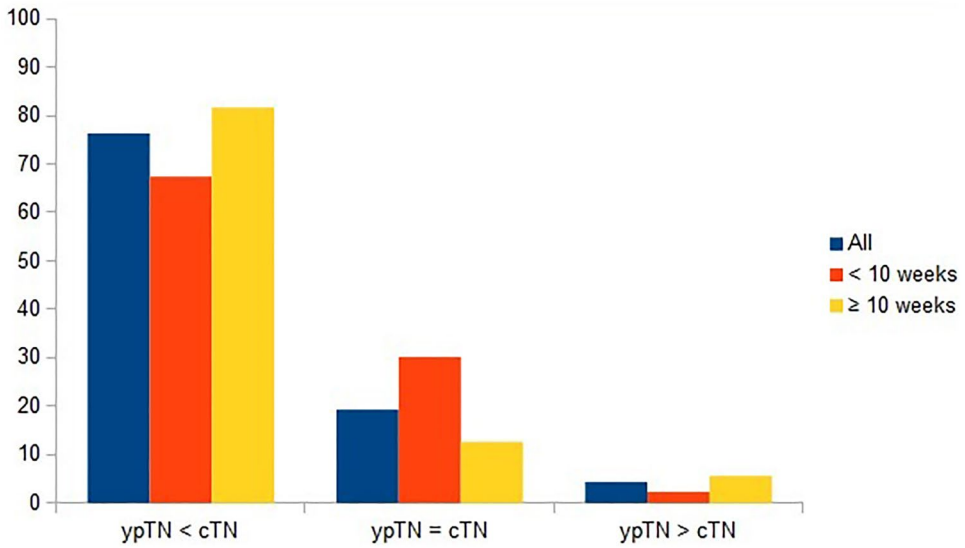

Fig. 3 Overall response rates comparing clinical with pathological stage, defining "response" as ypTN < cTN, "stable disease" as ypTN = cTN and "progression" as ypTN ≥ cTN

end of CRT and surgery (< 10 weeks versus ≥ 10 weeks) in 232 patients with LARC; patients who undergo surgery after ≥ 10 weeks of the end of chemoradiotherapy resulted four times more likely to achieve complete tumor remission without compromise surgical safety or postoperative morbidity [14]. In a pooled analysis of 3085 patients from seven randomized trials, Gambacorta et al. [15] suggested that the best time to achieve pCR in LARC is at 10 weeks, considering that the lengthening of surgical interval is not detrimental concerning survival outcomes. Therefore, our findings are in line with available literature.

In the study of Sloothaak et al., tumor, nodal, and combined TN downstaging were evaluated [13]. Similarly, in our study, we conducted this analysis showing a percentage of patients with T downstaging significantly greater in the group underwent surgery at ≥ 10 weeks after preoperative treatment (59.2%) compared to the patients with a waiting interval of less than 10 weeks (39.5%). Considering combined TN downstaging, there is a trend to a significant better response rate (ypTN less than cTN) increasing the interval to surgery, with rates of 81.7% and 67.4% ($p = 0.059$) in the 2nd and the 1st group, respectively.

There are some limitations of our study. First, this is a retrospective non-randomized analysis conducted in a single Institution. Second, we chose 10 weeks as the cut-off to divide the two groups, according principally to our clinical practice. However, there were no significant differences between the two groups regarding clinical characteristics and during the years, patients were treated by the same team of oncologists, radiation oncologists, and surgeons. Moreover, the chosen time interval is in line with literature.

In conclusion, our results show that prolonging the interval between the end of CRT and surgery (≥ 10 weeks) increases pathological response rates. Prospective randomized trials, like the ongoing TiMiSNAR trial, are necessary to better define the best interval between preoperative treatment and total mesorectal excision [22].

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by CP, LPS, GM, FV, DC, SF, MP, ETFP, and LR. The first draft of the manuscript was written by CP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Research involving human participants and/or animals The authors declare under their responsibility that the present study complies with the guidelines for human studies.

Ethics approval This study was done in compliance with ethical standards.

Informed consent As a retrospective analysis, informed consent was waived.

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