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Impact of Interval Between Neoadjuvant Chemoradiotherapy and Surgery for Rectal Cancer on Surgical and Oncologic Outcome

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Background: The aim of this study was to evaluate the effect of a longer interval between long-course neoadjuvant chemoradiotherapy and surgery on surgical and oncologic outcome.

Methods: A total of 233 consecutive patients with clinical stage II and III rectal cancer were divided into 2 groups according to the neoadjuvant–surgery interval: short-interval group ($\leq$7 weeks, n = 111), and long-interval group (>7 weeks, n = 122). Data on neoadjuvant–surgery interval, operative time, perioperative complications, final pathology, disease recurrence, and mortality were prospectively collected and analyzed.

Results: The two groups were comparable in terms of demographics, tumor, and treatment characteristics. Operative time and perioperative complications were not influenced by a longer interval. Patients in the long-interval group had a significantly higher pathologic complete response (pCR) rate (27.1% vs. 15.3%, $P = 0.029$), and a decreased rate of circumferential resection margin involvement (1.6% vs. 8.1%, $P = 0.020$). After a median follow-up of 42 months (range 6–90 months), the 3-year local recurrence rate was 12.9% in the short-interval group versus 4.8% in the long-interval group ($P = 0.025$).

Conclusions: A neoadjuvant–surgery interval >7 weeks is safe and is associated with a higher rate of pCR and R0 resection, and decreased local recurrence.

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KEY WORDS: rectal cancer; neoadjuvant therapy; interval; pathologic complete response; prognosis

INTRODUCTION

Neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) has become the standard of care for patients with locally advanced rectal cancer. Preoperative CRT is associated with better local control and increased treatment compliance compared to postoperative CRT [1,2].

One of the unsolved questions concerning neoadjuvant CRT is the optimal interval between neoadjuvant CRT and surgery. In 1999, Francois et al. [3] conducted a randomized trial (the Lyon R90-01 randomized trial), and showed that an interval of 6–8 weeks provided increased tumor downstaging without detrimental effect on toxicity and early clinical results compared to a 2- to 3-week interval. Based on these equivocal findings, an interval of 6–8 weeks between neoadjuvant CRT and surgery has become standard practice. However, the optimal interval between neoadjuvant CRT and surgical resection remains debated. A longer interval may result in increased shrinkage of the tumor and improve R0 resection rate. Some small studies showed that a longer interval was associated with increased tumor downstaging, higher rate of pCR, and decreased recurrence [4–8]. Furthermore, a "wait-and-see" approach has been successfully practiced in patients with clinical complete response (cCR) after neoadjuvant CRT, timing is of great importance for making such decisions [9,10].

This study was designed to investigate the influence of interval between neoadjuvant CRT and surgery on the following parameters: perioperative morbidity and mortality, postoperative recovery of gastrointestinal function, R0 resection rate, pathologic response, local and distant recurrence, disease-free survival (DFS), and overall survival (OS).

PATIENTS AND METHODS

We performed a retrospective review of a prospectively entered database, a total of 255 consecutive patients with clinical stage II and III, low (0–5 cm from the anal verge) and mid- (6–10 cm from the anal verge) rectal adenocarcinoma who underwent neoadjuvant therapy followed by radical resection with TME from January 2005 to December 2012 were identified. Twenty-two patients were excluded from the analysis: 10 patients were lost to follow-up, 8 only received neoadjuvant radiotherapy without chemotherapy, and 4 underwent R2 resection.

The following data were reviewed through our prospectively entered database: gender, age, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, clinical T and N stage, pretreatment distance from the anal verge, CRT regimen, the interval between CRT and surgery, intraoperative complications, operative time, estimated blood loss, postoperative recovery of gastrointestinal function, length of hospital stay, postoperative morbidity and mortality, and final pathologic stage.

All patients received digital rectal examination, colonoscopy with biopsy, abdominal and pelvic computed tomography (CT), and chest X-ray for clinical staging. Transrectal ultrasonography was performed in 188 (80.7%) patients, and 190 (81.5%) patients received pelvic magnetic resonance imaging for preoperative staging. Preoperative CRT was delivered to patients who had a clinical stage of T3 or T4 and/or positive lymph nodes.

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The details on radiotherapy have been previously published [11]. In brief, a total irradiation dose of 50.0 Gy was delivered in 2.0-Gy daily fractions to the pelvic area. Capecitabine was administered concurrently with radiotherapy at a dose of 1,600 mg/m^2/day for 35 days. Surgery was initially planned to perform 6–8 weeks after the completion of preoperative therapy irrespective of clinical tumor stage or response to CRT. Due to logistical factors, such as hospital bed availability, surgeons' and patients' scheduling preferences, actual intervals were varied. All patients underwent curative resection, and TME principle was followed for each patient. Postoperative morbidity and mortality were monitored for 30 days after surgery.

Postoperative specimens were examined by at least two pathologists specialized in colorectal cancer. Intraoperative perforation was defined as unintended perforation of the tumor or the adjacent bowel during surgery. CRMs were considered involved when a microscopic tumor was $\leq$1 mm from the mesorectal fascia. pCR (ypT0N0) was defined as absence of viable carcinoma cells in the surgical specimen, including primary tumor and lymph nodes. Tumors were staged according to the American Joint Committee on Cancer (seventh edition) staging system.

After hospital discharge, patients were suggested to visit doctors every 3 months within first 2 years and every 6 months thereafter. During each follow-up, patients received a series of evaluations, including digital rectal examination, complete blood count, liver function test, and carcinoembryonic antigen (CEA) level test. Abdominal and pelvic computed tomography (CT), and chest X-ray were performed every 6 months after surgery. Colonoscopy was performed per year after surgery.

Statistical Analysis

Continuous variables were expressed as median and range, and were analyzed with the Mann–Whitney *U*-test, while categorical ones were expressed as numbers with percentages, and were analyzed by Chi-square test or Fisher's exact test when appropriate. OS was defined from the date of operation to the date of death. Recurrence was defined by either imaging studies or pathological findings. DFS was defined as the time from operation to local recurrence, metastasis, or death. Kaplan–Meier method was used to analyze survival of patients, and comparisons were analyzed by log-rank test. All statistical tests were two-sided, and a *P*-value of less than 0.05 was considered statistically significant. Data were analyzed by Statistical Package for the Social Science (SPSS) 18.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Patient Demographics

A total of 233 consecutive patients who underwent neoadjuvant CRT followed by TME for clinical stage II or III rectal adenocarcinoma were included in this study. There were 130 (55.8%) males and 103 (44.2%) females. The median age was 59 years (range 26–86 years). Eighty-one (34.8%) patients had a tumor located between 0 and 5 cm from anal verge, and 152 (65.2%) patients had a tumor located between 6 and 10 cm form anal verge. Sixty (25.8%) patients had clinical stage II tumors, and 173 (74.2%) patients had clinical stage III tumors. The median interval between completion of CRT to surgery was 50 days (range 25–105 days). There were 111 (47.6%) patients in the group with an interval $\leq$7 weeks and 122 (52.4%) in the interval >7 weeks. The demographics and clinical characteristics were comparable between the two groups as detailed in Table I.

Surgical Characteristics and Perioperative Morbidity

Surgical characteristics are detailed in Table II. Sixty-six (59.5%) patients underwent sphincter-preserving surgery in the short-interval group and 80 (65.6%) patients in the long-interval group ($P = 0.335$). The operative time and estimated blood loss were not significantly influenced by the interval between CRT and surgery. One (0.9%) patient had intraoperative complication in short-interval group and 2

TABLE I. Demographics and Clinical Characteristics

Characteristic	Interval $\leq$7 weeks (n = 111)	Interval >7 weeks (n = 122)	*P*-Value
Interval (day)	43 (25–49)	59 (50–105)	<0.001
Female/male	49:62	54:68	0.986
Age (year)	59 (26–85)	59 (29–86)	0.674
BMI (kg/m^2)	23.7 (17.6–31.4)	23.6 (17.4–32.2)	0.645
ASA scores			0.231
1	15 (13.5%)	21 (17.2%)	
2	67 (60.4%)	60 (49.2%)	
3	29 (26.1%)	41 (33.6%)	
Distance from anal verge (cm)			0.697
0–5	40	41	
6–10	71	81	
cT stage			0.414
2	15 (13.5%)	14 (11.5%)	
3	82 (73.9%)	85 (69.7%)	
4	14 (12.6%)	23 (18.9%)	
cN stage			0.361
N0	32 (28.8%)	28 (23.0%)	
N1	60 (54.1%)	65 (53.3%)	
N2	19 (17.1%)	29 (23.8%)	
cTNM stage			0.305
2	32 (28.8%)	28 (23.0%)	
3	79 (71.2%)	94 (77.0%)	
Postoperative chemotherapy	76 (68.47%)	89 (72.95%)	0.452

BMI, body mass index; ASA, American Society of Anesthesiologists.

TABLE II. Surgical Characteristics and Postoperative Recovery

Characteristic	Interval $\leq$7 weeks (n = 111)	Interval >7 weeks (n = 122)	*P*-Value
Surgical procedure			0.335
APE	45 (40.5%)	42 (34.4%)	
LAR	66 (59.5%)	80 (65.6%)	
Diverting ostomy	54 (81.8%)	69 (86.3%)	
Operative time (min)	200 (120–280)	210 (120–320)	0.230
Estimated blood loss (ml)	150 (50–800)	150 (50–1500)	0.579
Intraoperative complications	1 (0.90%)	2 (1.64%)	0.934
Ureteral injury	1 (0.90%)	1 (0.82%)	0.520
Vagina injury	0 (0%)	1 (0.82%)	1
Postoperative complications	23 (20.7%)	30 (24.5%)	0.482
Anastomotic leakage	2 (3.03%)	3 (3.75%)	0.827
Cardiopulmonary	4 (3.60%)	7 (5.74%)	0.443
Wound dehiscence	7 (6.31%)	6 (5.08%)	0.690
Wound infection	3 (2.70%)	4 (3.28%)	0.899
Intestinal obstruction	3 (2.70%)	3 (3.75%)	0.767
Deep vein thrombosis	0 (0%)	1 (0.01%)	1
Retention of urine	5 (4.50%)	8 (6.56%)	0.495
Other	3 (2.70%)	5 (4.10)	0.823
Reoperation	4 (3.60%)	7 (5.74%)	0.443
Mortality	0 (0%)	0 (0%)	NA
Time to pass first flatus (day)	3 (1–5)	3 (1–5)	0.906
Time to pass first stool (day)	5 (2–10)	5 (2–9)	0.993
Time to start liquid diet (day)	3 (2–7)	3 (2–7)	0.982
Time to start normal diet (day)	5 (3–9)	5 (3–9)	0.929
Length of hospital stay (day)	10 (6–26)	10 (6–60)	0.380

APE, abdominoperineal excision; LAR, low anterior resection; NA, not available.

(1.64%) patients in the long-interval group ($P = 0.934$). The overall rates of postoperative complication were not significantly different between both groups, 20.7% in the short-interval group versus 24.5% in the long-interval group ($P = 0.482$). Eleven (4.7%) patients required reoperation, four (3.6%) in the short-interval group and seven (5.7%) in the long-interval group ($P = 0.443$). No patients died within 30 days after surgery. Postoperative return of gastrointestinal function and length of hospital stay were similar between both groups.

Pathologic Response

The median number of harvested lymph nodes was not affected by the length of interval, 12 in the short-interval group and 11 in the long-interval group ($P = 0.636$). Final pathologic tumor staging was ypT0 in 53 (22.7%) patients, ypTis in 4 (1.7%) patients, ypT1 in 23 (9.9%) patients, ypT2 in 61 (26.2%) patients, ypT3 in 87 (37.3%) patients, and ypT4 in 5 (2.1%) patients. Seventy-three (31.3%) patients were found to have lymph node involvement, N1 in 52 (22.3%) patients and N2 in 21 (9.0%)patients. Fifty (21.5%) patients achieved pCR. A longer interval was significantly associated with higher rate of pCR compared to short interval (27.1% vs. 15.3%, $P = 0.029$). Comparing pathological findings with clinical status based on imaging, higher rate of downstaging for both tumor (65.6% vs. 50.5%, $P = 0.019$) and node (53.3% vs. 38.7%, $P = 0.026$) category were observed in long-interval group. Response rates based on combined TN stage did not differ significantly between two groups. Rate of circumferential resection margin (CRM) involvement was significantly lower in the long-interval group (1.6% vs. 8.1%, $P = 0.020$). Intraoperative bowel perforation, lymphovascular and perineural invasion were similar between both groups (Table III).

TABLE III. Pathologic Characteristics

Characteristic	Interval ≤7 weeks (n = 111)	Interval >7 weeks (n = 122)	*P*-Value
ypT stage			0.039
T0	18 (16.2%)	35 (28.7%)	
Tis	2 (1.8%)	2 (1.6%)	
T1	10 (9.0%)	13 (10.7%)	
T2	25 (22.5%)	36 (29.5%)	
T3	53 (47.7%)	34 (27.9%)	
T4	3 (2.7%)	2 (1.6%)	
ypN stage			0.497
N0	72 (64.9%)	88 (72.1%)	
N1	28 (25.2%)	24 (19.7%)	
N2	11 (9.9%)	10 (8.2%)	
ypTNM stage			0.036
0	19 (17.1%)	35 (28.7%)	
1	27 (24.3%)	37 (30.3%)	
2	26 (23.4%)	16 (13.1%)	
3	39 (35.1%)	34 (27.9%)	
pCR (ypT0N0)	17 (15.3%)	33 (27.1%)	0.029
T downstaging (ypT < cT)	56 (50.5%)	80 (65.6%)	0.019
N downstaging (ypN < cN)	43 (38.7%)	65 (53.3%)	0.026
Tumor response			0.207
Response (ypTN < cTN)	69 (62.2%)	89 (73.0%)	
Stable disease (ypTN = cTN)	34 (30.6%)	26 (21.3%)	
Progression (ypTN > cTN)	8 (7.2%)	7 (5.7%)	
Number of harvested LNs	12 (1–42)	11 (0–50)	0.636
Number of positive lymph nodes	0 (0–18)	0 (0–22)	0.255
Intraoperative perforation	3 (2.7%)	4 (3.3%)	0.899
CRM involved	9 (8.1%)	2 (1.6%)	0.020
Lymphovascular invasion	18 (16.2%)	24 (19.7%)	0.493
Perineural invasion	13 (11.7%)	12 (9.8%)	0.644

CRM, circumferential resection margin.

Oncologic Outcomes

Postoperative chemotherapy was suggested to patients based on preoperative clinical staging irrespective of pathological staging. Finally, 165 (70.8%) patients received adjuvant chemotherapy, 76 in the short-interval group, 89 in the long-interval group ($P = 0.452$). The median follow-up period was 42 months (range 6–90 months). In the short-interval group, median follow-up was 40 months (range 6–90 months), and 43.5 months (range 6–86 months) in the long-interval group ($P = 0.341$). Local recurrence was observed in 18 (7.7%) patients, 13 patients in the short-interval group, and 6 patients in the long-interval group. The estimated 3-year local recurrence rate was 12.9% (95% confidence interval [CI] 6.0–19.8) in the short-interval group, and 4.8% (95% CI 0.7–8.9) in the long-interval group (Fig. 1, $P = 0.025$). Distant recurrent disease was observed in 38 (17.0%) patients, 19 patients in the short-interval group, and 19 patients in the long-interval group. The estimated 3-year distant recurrence rate was not significantly different between groups, 14.4% (95% CI 7.3–21.5) in the short-interval group versus 12.6% (95% CI 6.1–19.1) in the long-interval group ($P = 0.651$). The 3-year DFS rate was 72.6% (95% CI 63.8–81.4) in the short-interval group versus 79.4% (95% CI 71.6–87.2) in the long-interval group ($P = 0.130$). The 3-year OS rates were similar between both groups, 89.0% (95% CI 82.5–95.5) in the short-interval group versus 94.5% (95% CI 90.2–98.8) in the long-interval group ($P = 0.679$).

DISCUSSION

The optimal interval between neoadjuvant CRT and surgery is debated. In this study, we evaluated the influence of interval between neoadjuvant CRT and surgical resection on pathologic response and on surgical and oncologic outcome. A consecutive series of 233 patients with locally advanced rectal adenocarcinoma treated by a standard protocol of long-course neoadjuvant CRT were included. Patients were divided into two groups according to the neoadjuvant–surgery interval: short-interval group (≤7 weeks), and long-interval group (>7 weeks). We found that a neoadjuvant–surgery interval >7 weeks did not increase complexity of surgical resection or perioperative complication rate, and postoperative return of bowel function was not affected by the length of interval. Furthermore, a longer interval is associated with a higher rate of pCR, and decreased CRM involvement and local recurrence rate.

Traditionally, surgeons are not willing to postpone surgery after neoadjuvant CRT, because surgical difficulty may increase and result in higher surgical morbidity due to tissue fibrosis and friability, and radiotherapy-induced tissue swelling and local inflammation [8,12]. Garcia-Aguilar et al. [7] found that surgeons reported higher degree of pelvic fibrosis in patients operated on 11 weeks compared with 6 weeks after CRT. However, the increase in fibrosis did not translate into a significant increase in technical difficulty of operation or the risk of postoperative complications. In our study, we showed that the proportion of patients undergoing sphincter-saving surgery, operative time, and estimated blood loss were similar between both groups. In turn, these results indicated that complexity of surgical resection was not influenced by a longer interval. Many other authors also found similar results [3–5,7,8]. Moore et al. [6] observed more frequent anastomotic leaks and pelvic abscesses among 73 patients undergoing surgery more than 44 days after chemoradiation. Nevertheless, we and other authors [4,5,7,8] showed that perioperative complication rates, in terms of anastomotic leaks or wound infection, were not significantly affected by the length of interval. We also demonstrated that return of bowel function and length of hospital stay were comparable between two groups.

Previous studies have demonstrated that tumor regression and radiation-induced necrosis are a time-dependent phenomenon [13–15].

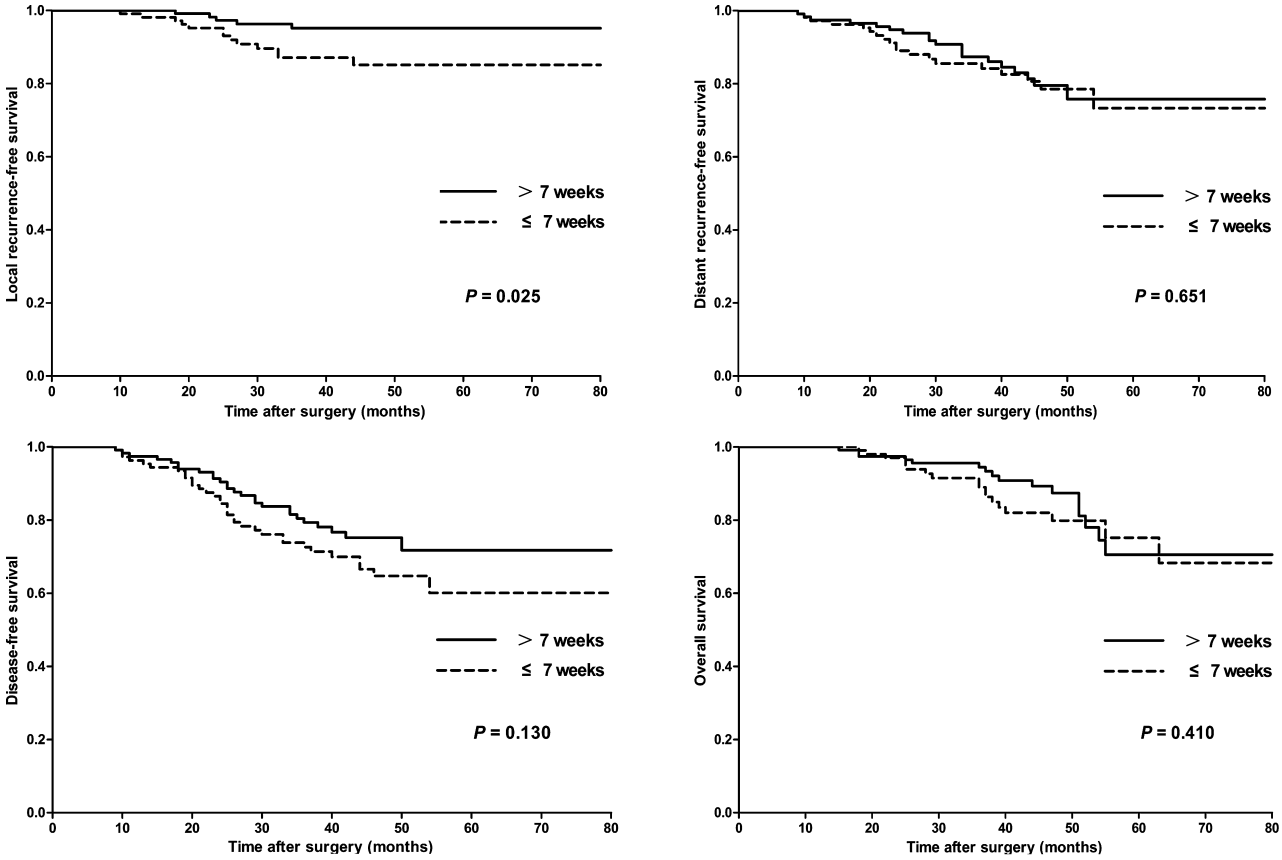

Fig. 1. Oncologic outcomes according to neoadjuvant–surgery interval.

Thus, a longer interval may allow the highest degree of tumor regression, and this will optimize the chance of an R0 resection. Indeed, we found that a longer interval was significantly associated with less CRM involvement, and higher rates of tumor downstaging and pCR. As CRM involvement is a well-know predictor for local recurrence, this maybe one of the reasons that local recurrence rate was significantly lower in the long-interval group. To the best of our knowledge, our study is the first to report that a longer interval between CRT and surgery is associated with a higher R0 resection rate. The possible reason is that most of previous studies do not specifically report on rates of resection margin involvement [3,5,13,16], and some studies may just do not have sufficient number of patients to achieve statistical significance [8,17].

Approximately 20% of rectal cancer patients undergoing neoadjuvant CRT achieve pCR, which has been associated with excellent long-term oncologic outcome [18,19]. Preliminary studies have shown that a wait-and-see policy can be safely applied to patients with a complete clinical response to neoadjuvant CRT [9,10]. Some studies try to improve tumor response by varying chemotherapy and radiation regimens, but none has found any significant impact on oncologic outcomes [20–23]. A longer interval between CRT and surgery may be a simple approach to improve tumor response and oncologic outcomes. We showed that a longer interval was significantly associated with a higher rate of pCR and better oncologic outcome. In accordance with our study, some other studies also find that longer interval between CRT and surgery improves tumor response and oncologic outcome [4,5,8]. De Campos-Lobato et al. [4] retrospectively divided 177 patients into 2 groups according to the time interval between completion of CRT and surgery (<8 weeks, n = 83; ≥8 weeks, n = 94). A longer interval led to a significant improvement in pCR rate (30.8% vs. 16.5%, $P = 0.03$) and decreased 3-year local recurrence rate (1.2% vs. 10.5%, $P = 0.04$). Kalady et al. [24] found that an interval ≥8 weeks between neoadjuvant CRT and surgical resection was the only predictor of pCR in 242 patients undergoing neoadjuvant CRT and surgery, which was associated with decreased local recurrence and improved OS.

About 30% patients in our study did not response to actual neoadjuvant CRT scheme, and approximate 6% patients even had tumor progression, which might have detrimental effects on tumor resectability and eventually negatively impact oncologic outcome. A longer interval creates the opportunity to add chemotherapy during the waiting period and this might be helpful to increase tumor response rates. In a preliminary study, 29 patients received 3 additional courses of 5-fluorouracil/leucovorin-based chemotherapy during the resting period, and 65% (19/29) patients achieved complete response with acceptable toxicity and high tolerability rates [25]. Garcia-Aguilar et al. [7] reported that adding two cycles of mFOLFOX-6 (folinic acid–fluorouracil–oxaliplatin) chemotherapy after CRT and delaying surgery from 6 to 11 weeks after CRT led to an increased pCR rate (18% vs. 25%) without affecting postoperative complications.

In the future, it may become routine to tailor the scheduling of surgery depending on the response to CRT. Patients that response well to CRT may delay surgical resection to achieve highest degree of tumor regression and improve R0 resection, and patients with a complete response may even undergo a wait-and-see policy, whereas patients that fail to response may require early resection or additional chemotherapy during the waiting period. As tumor regression is a time-dependent phenomenon, it is important to know when to reassess the tumor clinically and radiographically to restage the rumor and optimize the therapeutic regimen [26,27].

There are several limitations in our study. Because this study was not prospectively designed, it is subject to potential bias. Although the patients were not prospectively matched, the demographics and clinical characteristics were comparable between the two groups. The length of interval was not affected by tumor stage or response, and the actual differences in the interval could be explained by logistical factors, such as hospital bed availability, operating theatre availability, and surgeons' and patients' scheduling preferences.

CONCLUSION

In conclusion, our study demonstrates that a neoadjuvant–surgery interval >7 weeks do not increase complexity of surgical resection or perioperative morbidity while yielding higher rate of pCR and R0 resection, and improved local control. A longer interval is safe and associated with better oncologic outcome.

REFERENCES

1. Fleming FJ, Påhlman L, Monson JR: Neoadjuvant therapy in rectal cancer. Dis Colon Rectum 2011;54:901–912.
2. Sauer R, Becker H, Hohenberger W, et al.: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–1740.
3. Francois Y, Nemoz CJ, Baulieux J, et al.: Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: The Lyon R 90-01 randomized trial. J Clin Oncol 1999;17:2396.
4. de Campos-Lobato LF, Geisler DP, da Luz Moreira A, et al.: Neoadjuvant therapy for rectal cancer: The impact of longer interval between chemoradiation and surgery. J Gastrointest Surg 2011;15: 444–4450.
5. Tulchinsky H, Shmueli E, Figer A, et al.: An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Ann Surg Oncol 2008;15:2661–2667.
6. Moore HG, Gittleman AE, Minsky BD, et al.: Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. Dis Colon Rectum 2004;47:279–286.
7. Garcia-Aguilar J, Smith DD, Avila K, et al.: Timing of Rectal Cancer Response to Chemoradiation Consortium. Optimal timing of surgery after chemoradiation for advanced rectal cancer: Preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 2011;254:97–102.
8. Wolthuis AM, Penninckx F, Haustermans K, et al.: Impact of interval between neoadjuvant chemoradiotherapy and TME for locally advanced rectal cancer on pathologic response and oncologic outcome. Ann Surg Oncol 2012;19:2833–2841.
9. Habr-Gama A, Perez RO, Nadalin W, et al.: Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: Long-term results. Ann Surg 2004;240: 711–717.
10. Maas M, Beets-Tan RG, Lambregts DM, et al.: Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633–4640.
11. Jin J, Li YX, Liu YP, et al.: A phase I study of concurrent radiotherapy and capecitabine as adjuvant treatment for operable rectal cancer. Int J Radiat Oncol Biol Phys 2006;64: 725–729.
12. Tran CL, Udani S, Holt A, et al.: Evaluation of safety of increased time interval between chemoradiation and resection for rectal cancer. Am J Surg 2006;192:873–877.
13. Habr-Gama A, Perez RO, Proscurshim I, et al.: Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: Does delayed surgery have an impact on outcome? Int J Radiat Oncol Biol Phys 2008;71:1181–1188.
14. Berger C, de Muret A, Garaud P, et al.: Preoperative radiotherapy (RT) for rectal cancer: Predictive factors of tumor downstaging and residual tumor cell density (RTCD): Prognostic implications. Int J Radiat Oncol Biol Phys 1997;37:619–627.
15. Horn A, Morild I, Dahl O: Tumour shrinkage and down staging after preoperative radiation of rectal adenocarcinomas. Radiother Oncol 1990;18:19–28.
16. Stein DE, Mahmoud NN, Anné PR, et al.: Longer time interval between completion of neoadjuvant chemoradiation and surgical resection does not improve downstaging of rectal carcinoma. Dis Colon Rectum 2003;46:448–453.
17. Evans J, Tait D, Swift I, et al.: Timing of surgery following preoperative therapy in rectal cancer: The need for a prospective randomized trial? Dis Colon Rectum 2011;54:1251–1259.
18. Maas M, Nelemans PJ, Valentini V, et al.: Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data. Lancet Oncol 2010;11:835–844.
19. Capirci C, Valentini V, Cionini L, et al.: Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: Long-term analysis of 566 ypCR patients. Int J Radiat Oncol Biol Phys 2008;72:99–107.
20. Chau I, Brown G, Cunningham D, et al.: Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. J Clin Oncol 2006;24:668–674.
21. Lawson JD, Kauh J, Koshy M, et al.: Early clinical results from chemoradiation with 5-fluorouracil and oxaliplatin for locally advanced rectal cancer. Clin Colorectal Cancer 2008;7:325–330.
22. Carlomagno C, Farella A, Bucci L, et al.: Neo-adjuvant treatment of rectal cancer with capecitabine and oxaliplatin in combination with radiotherapy: A phase II study. Ann Oncol 2009;20:906–912.
23. Rosenthal DI, Catalano PJ, Haller DG, et al.: Phase I study of preoperative radiation therapy with concurrent infusional 5-fluorouracil and oxaliplatin followed by surgery and postoperative 5-fluorouracil plus leucovorin for T3/T4 rectal adenocarcinoma: ECOG E1297. Int J Radiat Oncol Biol Phys 2008;72:108–113.
24. Kalady MF, de Campos-Lobato LF, Stocchi L, et al.: Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. Ann Surg 2009;250:582–589.
25. Habr-Gama A, Perez RO, Sabbaga J, et al.: Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: Results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum 2009;52:1927–1934.
26. Habr-Gama A, Perez RO, Wynn G, et al.: Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: Characterization of clinical and endoscopic findings for standardization. Dis Colon Rectum 2010;53:1692–1698.
27. O'Neill BD, Brown G, Heald RJ, et al.: Non-operative treatment after neoadjuvant chemoradiotherapy for rectal cancer. Lancet Oncol 2007;8:625–633.