Original Article

Prolonging the Interval between Neoadjuvant Concurrent Chemoradiotherapy and Surgery Improves Pathological Outcomes in Rectal Cancer

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Key Words
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Purpose. Preoperative neoadjuvant concurrent chemoradiotherapy (CCRT) followed by a radical operation has become a standard procedure for locally advanced low rectal cancer. However, the optimal interval between the end of neoadjuvant CCRT and the operation is still controversial. This retrospective analysis is aimed to demonstrate the impact of prolonging this interval on pathological outcomes.

Methods. Eighty-five patients with locally advanced rectal cancer who had undergone neoadjuvant CCRT followed by surgical interventions between 2010 Feb to 2014 Aug were included. Data on clinical TNM stage before treatment, interval between neoadjuvant therapy and surgery, type of surgery, and final pathologic stage were collected and analyzed.

Results. Patients were divided into two groups according to the interval between neoadjuvant therapy and surgery: shorter interval group (< 10 weeks, n = 54), and longer interval group (≧ 10 weeks, n = 38). There was no significant difference in demographics, TNM stage before treatment, and type of surgery between these 2 groups. The group with longer intervalshad significantly higher nearly pathological complete response (22.2% vs.45.2%, $p = 0.049$).

Conclusion. Longer interval (≧ 10 wks) between the end of neoadjuvant CCRT and surgery seems to improve the pathologic outcomes. The nearly complete response rate was significantly higher in the longer interval group.

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Radical surgery is the mainstream in the treatment of resectable rectal cancer. Besides, for patients with locally advanced rectal cancer, concurrent chemoradiotherapy (CCRT) accompanied with radical surgery has been proven to decrease local recurrence. Comparing to postoperative adjuvant chemoradio-

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therapy, preoperative neoadjuvant chemoradiotherapy was associated with better local control and lower toxicities.[1,2] Therefore, a neoadjuvant CCRT followed by a total mesentery excision (TME) has been widely used currently.

However, the optimal surgical timing is still under debate. In 1999, Francois et al. published a randomized study, which reported that compared to a 2-4 week interval, alonger interval of 6-8 weeks improved tumor downstaging without compromising early clinical outcomes or toxicities.[3] Since this so-called "Lyon trail", the interval of 6 to 8 weeks has been set as a standard in clinical practices, although recent studies have shown conflicting results in the impact of intervals between radiation and surgery on tumor response.[4-8] Theoretically, tumor regression is a time-dependent progress, and therefore prolonged intervals between CCRT and surgery may provide better chance of tumor downstaging and pathological complete response (pCR). Furthermore, nonoperative management, so-called "wait-and-see" policy, or local excision of postradiative scarhave been observed with feasible outcomes in highly selected patients with clinical complete response.[9]

This study aims to analyze whether prolonged intervals between neoadjuvant CCRT and surgery increase tumor regression and further improve pathological outcomes in patients with locally advanced rectal cancer.

Methods

Patients

We performed a retrospective review. All patients with locally advanced rectal cancer (T3, T4, or any T with positive N stage) who had underwent long course radiotherapy and concurrent 5-Fu based chemotherapy between February 2010 and August 2014 in our institute were identified. A total of 108 patients were identified. Of these, 23 patients were excluded; three had incomplete RT courses, and 20 were excluded because the patient was unwilling to undergo the radical operation after the neoadjuvant therapy.

The following data have been reviewed: gender, age, BMI, tumor location, clinical stage including T, N, and M, surgical procedure, the creation of diverting stoma, neoadjuvant regimen, and the interval between the end of neoadjuvant radiation and the operation.

For staging workups, all patients underwent physical examination including digital rectal examination, chest X-ray, abdominal computed tomography (CT) and pelvic CT before the neoadjuvant radiotherapy started. A colonoscopy was performed in every patient for pathology proof and to exclude synchronous lesions.

Preoperative chemoradiotherapy

All patients underwent neoadjuvant CCRT. Five patients received 3750 cGy/15 fractions, one patient received 4400 cGY/22 fractions, and the rest 79 patients received 5040 cGy/28 fractions.

Chemotherapy was prescribed concurrently with radiotherapy. Of all patients, 59 underwent Rosewell Park regiment (500 mg/m2, weekly), 10 underwent Mayo clinic regiment (425 mg/m2 for 5 days), and 16 underwent oral form Uracil/Tegafur (Ufur).

Surgical resection & pathology

According to the NCCN clinical practice guidelines for rectal cancer, we tend to perform surgery 5 to 10 weeks after the end of neoadjuvant radiation.[10] However, because of logistical factors, such as hospital bed availabilities and surgeons' or patients' scheduling, the practical intervals were varied. All operations were performed by surgeons subspecialized in colorectal cancer. All patients underwent curative operation and total mesentery excision (TME) principle was strictly adhered. All specimens were reviewed by pathologists specializing in colorectal cancer.

Statistical analysis

Statistical analyses performed for group comparison were independent t test, Fisher's exact test, or Mann-Whitney U test, depending on the nature of variables. Significant results were considered for $p < 0.05$.

Results

Demographics, clinical staging and surgical characteristics

Overall, eighty-five patients were eligible for this study. There were 64 males (75.3%) and 21 females (24.9%). The median age was 61 years, and the median body mass index (BMI) was 23.9 Kg/m2. Fifty-six patients (65.9%) had the tumor located in the lower rectum (0 to 5 cm above the anal verge). The median tumor location was 5 cm (range from 2 to 15 cm). Thirty-two patients (37.6%) were clinical stage II, and 53 patients (62.4%) were clinical stage III. The median interval between the completion of neoadjuvant CCRT and the surgery range was 55 days.

Of all 85 patients, fifty-four patients (58.7%) hadan interval between the end of radiation and surgery of less than 10 weeks, and 31 patients hadan interval equal to or greater than 10 weeks. The distribution of the interval between the end of the radiation and surgery is shown in Fig. 1. Baseline characteristics were similar in two groups: there was no difference in gender, age, body mass index (BMI), American Society of Anesthesiologists (ASA) scores, tumor location or clinical TNM stage (Table 1).

Two patients (2.4%) developed distant metastasis

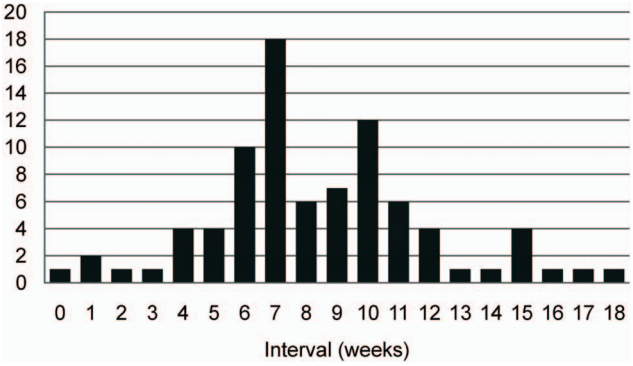

Fig. 1. Distributions of the interval between the end of radiation and surgery.

Table 1. Demographics and clinical characteristics

Characteristic	Interval < 10 weeks (n = 54)	Interval ≧ 10 weeks (n = 31)	*p*-value
Interval, days (IQR)	48 (40-51)	80 (71-98)	< 0.001
Gender			1
Female	13 (24.1%)	8 (25.8%)	
Male	41 (75.9%)	23 (74.2%)	
Age, years (±SD)	58 (±11.7)	68 (±12.3)	0.884
BMI, kg/m2 (±SD)	23.7 (±3.6)	24.7 (±4.1)	0.466
Distance from anal verge			0.508
Low (0-5 cm)	38 (70.4%)	18 (68.1%)	
Medium (6-10 cm)	15 (27.8%)	12 (38.7%)	
Upper (> 10 cm)	1 (1.9%)	1 (3.2%)	
ASA scores			
1	1 (1.9%)	0 (0%)	0.692
2	39 (72.2%)	24 (77.4%)	
3	14 (25.9%)	7 (22.6%)	
cT stage			0.04
2	4 (7.4%)	1 (3.2%)	
3	33 (61.1%)	27 (87.1%)	
4	17 (31.5%)	3 (9.7%)	
cN stage			0.711
0	22 (40.7%)	10 (32.3%)	
1	21 (38.9%)	13 (41.9%)	
2	11 (20.4%)	8 (25.8%)	
cTNM stage			0.49
II	22 (40.7%)	10 (32.3%)	
III	32 (59.3%)	21 (67.7%)	

IQR: Interquartile range; SD: standard deviation; BMI: body mass index; ASA: American Society of Anesthesiologists.

after neoadjuvant chemotherapy. Seven patients (8.2%) underwent abdominoperineal resection, and 78 patients (84.8%) underwent low anterior resection. Diverting stoma rate was 97.3% (76 patients) in patients undergoing LAR. The median estimated blood loss during the operation was 150 ml, and the median operative time was 244 minutes (Table 2).

Pathologic response

The median interval between radiation and the operation was 48 days in the shorter interval group, and 80 days inthe longer interval group. Pathological tumor stagings were ypT0 in 25 patients (29.4%), ypTis in 1 (1.2%), ypT1 in 1 (1.2%), ypT2 in 21 (24.7%), ypT3 in 31 (36.5%), and ypT4 in 6 (7.1%). Regional lymph node involvement was noted in 25 out of 85 specimens (29.4%). Though not attaining statistical significance, higher pathology complete response (pCR, i.e., ypT0) was observed in the longer interval group (41.9% versus 22.2%, $p = 0.083$). Nearly complete response (i.e., ypT0-1) was significantly higher in the group with longer interval (45.2% versus 22.2%, $p = 0.049$). There was no statistic difference in T downstaging (ypT stage < cT stage), or N downstaging (ypN stage < cN stage) in both groups. The details are shown in Table 3.

Discussion

Optimal intervals between neoadjuvant CCRT and radical surgery is still under debate. In 1999, Francois et al published a randomized control trial, which showed that longer intervals (6-8 wk) between neoadjuvant radiotherapy and TME has better nearly complete response (ypT0-1N0) with no difference in postoperative morbidity comparing to the shorter interval group (< 2 wk).[3] Since then, the 6-8 weekinterval between neoadjuvant CCRT and surgery has been routinely practiced in locally advanced rectal cancer.

Recently, some studies have suggested that tumor downstaging is a time-dependent process.[7,11,12] That means the intervals between CCRT and radiation may be associated with the tumor regression. Several previous studies have shown that compared to the shorter interval, the longer interval has better pCR rate.[5,8] Another previous study also showed that the intervals between radiotherapy and surgery are the only predictive factor for pCR after multivariable analysis.[13] Our study demonstrated that higher pCR could be achieved when the interval between radiation and surgery is greater than 10 weeks, which is consistent with other previous studies.[14]

Pathologically complete response pCR after neoadjuvant radiation in rectal cancer has been disclosed from 10% to 26% in individual studies.[15] For instance, Albert M. Wolthuis et al. And WEI-GEN ZENG et al. reported pCR in 22% and 22.7% patients after neoadjuvant radiotherapy. In our study pCR rate was 29.4%, which was inconsistently higher compared to these two studies.[16,17] However, when we compared nearly completely response (ypT0, ypTis, or ypT1) rates, the results were very similar (31% in our study versus 34.3% in Wolthuis' study). This may imply that the inconsistence of pCR is a pathological issue. The definition of pathological complete response varies in previous individual studies,[18] and the difference between complete response scar and ypT1 is

Table 2. Surgical procedures and perioperative parameters

Characteristic	Interval < 10 weeks (n = 54)	Interval ≧ 10 weeks (n = 31)	*p*-value
Surgical procedure			0.414
APR	6 (11.1%)	1 (3.2%)	
LAR	48 (88.9%)	30 (96.8%)	
Diverting stoma	46 (95.8%)	30 (100%)	0.520
Estimated blood loss, ml (IQR)	190 (88-388)	100 (50-237)	0.056
Operative time, min (IQR)	250 (215-319)	244 (221-325)	0.884

APR, abdominoperineal resection. LAR, low anterior resection. TEM, transanal endoscopic microsurgery. IQR, Interquartile range.

Table 3. Pathologic characteristics

Characteristic	Interval < 10 weeks (n = 54)	Interval ≧ 10 weeks (n = 31)	*p*-value
ypT stage			0.118
T0	12 (22.2%)	13 (41.9%)	
Tis	0 (0.0%)	1 (3.2%)	
T1	0 (0.0%)	1 (3.2%)	
T2	16 (29.6%)	5 (16.1%)	
T3	21 (38.9%)	10 (32.3%)	
T4	5 (9.1%)	1 (3.2%)	
ypN stage			0.110
N0	38 (70.4%)	22 (71%)	
N1	10 (18.5%)	9 (29%)	
N2	6 (11.1%)	0 (0.0%)	
pCR (ypT0N0)	12 (22.2%)	13 (41.9%)	0.083
pCR and near pCR (ypT0-TisN0)	12 (22.2%)	14 (45.2%)	0.049
Number of harvest LNs*	10.8 (8.7-12.7)	7 (5-9)	0.107
Differentiation			0.086
Well-to-moderate	42 (100%)	16 (88.9%)	
Poor	0 (0%)	6.5% (11.1)	
T down staging (ypT < cT)	34 (63%)	21 (67.7%)	0.814
N down staging (ypN <cN)	22 (40.7)	17 (54.8%)	0.260
Distant metastasis after RT	1 (1.9%)	1 (3.2%)	1
Lymphovascular invasion†	4 (10%, n = 40)	1 (5.6%, n = 18)	1
Perineural invasion†	9 (22.5%, n = 40)	1 (5.6%, n = 18)	0.150

* Values are mean (95% CI). † Lymph-vascular and perineural invasion cannot be acquired in some of the cases because they're not checked routinely in our institute. LNs, lymph nodes. RT, radiotherapy.

ambiguous. Nevertheless, our study still suggests that prolonged intervals didimprove pathological response significantly.

Traditionally, surgeons have been reluctant to postpone the operation after radiation because of the concerns about post-radiative fibrosis, inflammatory change and tissue swelling. Garcia-Aguilar et al. found that degree of pelvic fibrosis is higher when the interval is prolonged to 11 weeks, compared to the shorter 6-week-interval. Despite that, there was no difference in surgical technical difficulty.[19] Operative time and blood loss is a surrogated indicator for surgical difficulty, and they both showed no statistical difference in our study. This implies that prolonging the interval is safe and may not increase surgical difficulty.

According to the NCCN guidelines for rectal cancer, we used to set the interval to 5-10 weeks in our institute. However, because of reasons like ward or operation room availability, surgeon's preference or patient's schedule, the intervals vary in clinical situation. Though our study showed that prolonging interval between neoadjuvant radiation and the surgery increased the pathological responses, the "optimal intervals" have not yet beendetermined. Neoadjuvant CCRT in rectal cancer has been proven to reduce the local recurrence rate compared to surgery alone.[20] Since tumor downstaging is a time-dependent process, theoretically prolonging intervals to optimize tumor downstaging can have better R0 resection rate and sphincter preservation. The frequency of sphincter-preservation is higher in the group with longer intervals in our study, which is consistent with this hypothesis. Furthermore, patients with pCR after neoadjuvant CCRT have been shown to have higher 5-year disease-free survival rates (83.3% vs. 65.6%) in a meta-analysis including 3056 patients with rectal cancer.[21] Even though, better pCR rate in longer interval groups cannot be translated to better oncological outcomes according to current publications. One of the explanations is that tumors which achieved pCR have favorable biological properties, and prolonged intervals provide a chance to identify them.[18,21,22]

Despite data about oncological outcomes still being conflicted, higher pCR rate after prolonged intervals is promising. This offers us a chance to tailor our management for individual patients. For example, some studies demonstrate that watch and wait or transanal endoscopic microsurgery for postradiation scar provided satisfactory outcomes in highly selected patients.[23-26] Besides, pCR can be even higher by adding induction chemotherapy. Garcia-Aguilar reported pCR rate is significantly increased by adding 2 cycles of FOLFOX after neoadjuvant radiation.[19] All this motivated us to individualize our schedules of surgery in each single patient according to our treatment goal and patients' response to the treatment. In patients who responded well to the radiation, a prolonged interval was suitable to achieve better tumor regression and patients with clinical complete response may even go for local excision or watch-and-wait policy in some highly selected situations.[9]

Since this is not a prospective design but a retrospective analysis, there are some limitations in our study, which we could not adjust for in our analysis. Potential bas exists in patient selection and surgeons' personal preference. For example, it is possible that surgeons were more likely to postpone the operation in the patients with better clinical response after radiation, thus biasing our results. Further prospective randomized trialsare needed to disclose the impact of intervals between radiation and surgery in surgical and oncological outcomes.

Conclusion

In conclusion, this retrospective study reveals that prolonging intervals to above 10 weeks between neoadjuvant concurrent chemoradiotherpy to surgery in locally advanced rectal cancer can achieve better pathological outcomes.

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原　著

延長直腸癌前導性化放療至手術前的間隔增進病理結果

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目的　術前的前導性合併化學及放射線治療加上根治性手術已經是目前對於局部侵犯的直腸癌中的標準治療。然而，在前導性合併化學及放射線與手術之間需間隔多久目前仍具爭議性。這篇回溯性分析的目的是展現延長前導治療與手術之間的間隔對術後病理結果的影響。

方法　自 2010 年二月到 2014 年八月為止，共 85 位接受過前導性化學放射治療及根治性手術的直腸癌病人被涵括入這項研究。治療前臨床 TNM 分期、放射治療結束到手術的時間、手術方式，以及術後病理分期都被收集與分析。

結果　根據放射治療結束與根治性手術之間的間隔長度，85 位病患分成兩組：短間隔組 (< 10 週，n ＝ 54) 以及長間隔組 (≧ 10 週，n ＝ 31)。病人特種、治療前分期，及手術方式兩組間無特別差異。在接近病理完全反應率 (ypT0-1N0) 方面長間隔組明顯優於短間隔組 (45.2% versus 22.2%, $p = 0.049$)。

結論　拉長前導性放射化學治療與根治性手術之間的間隔似乎能增進病理結果。長間隔組的接近病理完全反應率明顯提高。

關鍵詞　直腸癌、前導性化學放射治療、手術間隔、病理結果。