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ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Dr. Lin is a distinguished professor at the Hebei Medical University in Shijiazhuang, China. Dr. Lin received his Bachelor's degree from Tianjin Medical University in 1998 and undertook his postgraduate training at Hebei Medical University, receiving his PhD in 2007. He rose to Chief Oncologist in the Department of Oncology, North China Petroleum Bureau General Hospital Affiliated to Hebei Medical University in 2013 and has held the position since. Further, he has served as one of the academic leaders of the five Key Developing Disciplines (Oncology) in Hebei Province since 2017. He also currently serves as Secretary General of the Clinical Committee of Anticancer Drugs, China Pharmaceutical Industry Research and Development Association. His ongoing research interests involve the application of evidence-based medicine in digestive oncology and thoracic oncology. (L-Editor: Filipodia)

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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ORIGINAL ARTICLE

Observational Study

Outcomes of neoadjuvant chemoradiotherapy followed by radical resection for T4 colorectal cancer

Chun-Ming Huang, Ching-Wen Huang, Cheng-Jen Ma, Hsiang-Lin Tsai, Wei-Chih Su, Tsung-Kun Chang, Ming-Yii Huang, Jaw Yuan Wang

ORCID number: Chun-Ming Huang 0000-0002-2605-9639; Ching-Wen Huang 0000-0001-8011-8428; Cheng-Jen Ma 0000-0001-8923-9912; Hsiang-Lin Tsai 0000-0002-1645-2525; Wei-Chih Su 0000-0002-9336-0667; Tsung-Kun Chang 0000-0001-9760-5070; Ming-Yii Huang 0000-0001-9432-5284; Jaw Yuan Wang 0000-0002-7705-2621.

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Chun-Ming Huang, Ming-Yii Huang, Department of Radiation Oncology, Kaohsiung Medical University Hospital, Kaohsiung 80145, Taiwan

Ching-Wen Huang, Hsiang-Lin Tsai, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 80145, Taiwan

Cheng-Jen Ma, Wei-Chih Su, Tsung-Kun Chang, Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung 80145, Taiwan

Jaw Yuan Wang, Department of Surgery and Cancer Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 80708, Taiwan

Corresponding author: Jaw Yuan Wang, MD, PhD, Professor, Department of Surgery and Cancer Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100 Tz-You 1st Road, Kaohsiung 80708, Taiwan. cy614112@ms14.hinet.net

Abstract

BACKGROUND

Patients with clinical T4 colorectal cancer (CRC) have a poor prognosis because of compromised surgical margins. Neoadjuvant therapy may be effective in downstaging tumors, thereby rendering possible radical resection with clear margins.

AIM

To evaluate tumor downsizing and resection with clear margins in T4 CRC patients undergoing neoadjuvant concurrent chemoradiotherapy followed by surgery.

METHODS

This study retrospectively included 86 eligible patients with clinical T4 CRC who underwent neoadjuvant concurrent chemoradiotherapy followed by radical resection. Neoadjuvant therapy consisted of radiation therapy at a dose of 45-50.4 Gy and chemotherapy agents, either FOLFOX or capecitabine. A circumferential resection margin (CRM) of < 1 mm was considered to be a positive margin. We defined pathological complete response (pCR) as the absence of any malignant cells in a specimen, including the primary tumor and lymph nodes. A multivariate logistic regression model was used to identify independent

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predictive factors for pCR.

RESULTS

For 86 patients who underwent neoadjuvant chemoradiotherapy and surgery, the rate of pCR was 14%, and the R0 resection rate was 91.9%. Of the 61 patients with rectal cancer, 7 (11.5%) achieved pCR and 5 (8.2%) had positive CRMs. Of the 25 patients with colon cancer, 5 (20%) achieved pCR and 2 (8%) had positive CRMs. We observed that the FOLFOX regimen was an independent predictor of pCR (P = 0.046). After a median follow-up of 47 mo, the estimated 5-year overall survival (OS) and disease-free survival (DFS) rates were 70.8% and 61.4%, respectively. Multivariate analysis revealed that a tumor with a negative resection margin was associated with improved DFS (P = 0.014) and OS (P = 0.001). Patients who achieved pCR exhibited longer DFS (P = 0.042) and OS (P = 0.003) than those who did not.

CONCLUSION

Neoadjuvant concurrent chemoradiotherapy engenders favorable pCR and R0 resection rates among patients with T4 CRC. The R0 resection rate and pCR are independent prognostic factors for patients with T4 CRC.

Key Words: T4; Chemoradiotherapy; Pathological complete response; R0 resection; Colorectal cancer; Survival

Core Tip: Patients with clinical T4 colorectal cancer have a poor prognosis because of compromised surgical margins. This retrospective study demonstrated that neoadjuvant chemoradiotherapy resulted in high rates of pathological complete response and complete resection for patients with T4 colorectal cancer. An aggressive approach that entails implementing the FOLFOX regimen before, during, and after irradiation is safe and can improve pathological complete response rates. Negative resection margins and pathological complete response are significantly associated with survival.

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INTRODUCTION

Colorectal cancer (CRC) is a major public health concern because of its high incidence and death rates in Western countries[1]. In Taiwan, CRC is the most commonly diagnosed cancer, with the number of patients with CRC increasing rapidly in recent years; CRC is also the third leading cause of cancer-related death in Taiwan[2]. Surgical resection with a free tumor margin (R0 resection) is a curative method for localized CRC. However, the resection of T4 CRC involves a high risk of positive surgical margins and local recurrence; therefore, patients with T4 CRC have relatively poor overall survival (OS) and disease-free survival (DFS)[3,4]. A study reported that patients with T4 CRC had a 5-year DFS rate of 75.4%, considerably lower than those for patients with T1-T3 tumors (T1: 98.8%; T2: 95.7; T3: 86.5%)[5].

R0 resection is a crucial prognostic factor in patients with CRC. Studies have reported that multivisceral resection (MVR) improves the prognosis of locally advanced CRC, but this is at the cost of increased morbidity and mortality[3,6]. Other studies have revealed that patients with locally advanced CRC who underwent MVR had R0 resection rates of 40%-90%[3,6,7]. Neoadjuvant concurrent chemoradiotherapy (CCRT) followed by surgical resection is the main treatment for locally advanced rectal cancer (LARC), and tumor downstaging may facilitate complete resection of T4 lesions[8,9]. However, administering neoadjuvant CCRT in patients with locally

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advanced colon cancer is controversial[10-12].

Patients achieving pathological complete response (pCR) experience more favorable oncologic outcomes compared with patients not[13,14]. Most studies have enrolled both patients with clinical T3 and those with T4 rectal cancer for the administration of neoadjuvant CCRT, but those with T4 disease usually exhibited more unfavorable responses to CCRT compared with those with T3 disease; this can be attributed to the extensive invasion of surrounding tissues and large tumor burden of T4 lesions that make radical resection difficult[15-17]. Research results or clinical evidence regarding pCR after the administration of neoadjuvant CCRT for clinical T4 (cT4) CRC is currently limited.

To address this gap in the literature, the present study was conducted to determine the oncologic results of neoadjuvant CCRT administration followed by radical resection and to identify predictive factors for pCR, DFS, and OS in patients with T4 CRC.

MATERIALS AND METHODS

Patients

We retrieved records of consecutive patients with cT4 CRC and biopsy-proven adenocarcinoma who underwent neoadjuvant CCRT followed by radical resection between August 2010 and September 2018. A cT4 stage was defined as radiological evidence of tumor penetration into the surface of the visceral peritoneum (T4a) or direct tumor invasion or adhesion to nearby organs (T4b). Patients with distant metastases at diagnosis and previous or synchronous malignancies were excluded from this analysis. This study was approved by our institutional review board. Cancer staging was determined according to abdominal computed tomography (CT) scans for colon cancer and pelvic magnetic resonance imaging (MRI) for rectal cancer. For patients with locally advanced colon cancer, the imaging studies and treatment strategies were reviewed by a multidisciplinary cancer team.

Preoperative chemotherapy

Patients underwent one of two preoperative chemotherapy regimens, namely, capecitabine and FOLFOX regimens. A total of 13 patients with cT4 CRC received the capecitabine regimen; specifically, these patients received capecitabine (850 mg/m^2) twice daily for 5 d/wk throughout the 5 wk of radiation therapy (RT). A total of 75 patients received the FOLFOX regimen, which entailed a biweekly schedule of FOLFOX. Each cycle of FOLFOX chemotherapy involved oxaliplatin (85 mg/m^2) and folinic acid (400 mg/m^2) infusion on day 1, followed by a 46-h infusion of 5-fluorouracil (2800 mg/m^2) repeated every 2 wk. Patients in the FOLFOX group received one or two cycles of induction FOLFOX before CCRT, followed by two cycles of FOLFOX concomitantly administered during RT and an additional three or four cycles of consolidation FOLFOX after CCRT.

Radiotherapy

Target volumes were determined in accordance with the principles of the International Commission on Radiation Units and Measurements Reports 50 and 62. The gross tumor volume (GTV) was defined as the volume of the visible tumor and enlarged lymph nodes apparent on diagnostic CT or MRI images. A 1.5-2 cm clinical target volume (CTV) margin was added to the GTV. In addition to the CTV, we added a planning target margin of 1-1.5 cm. Irradiation was delivered at a total dose of 45-50.4 Gy with a daily fraction of 1.8 Gy or 2.0 Gy.

Surgical and pathological review

Patients underwent radical resection after completing neoadjuvant treatment. For colon cancer, hemicolectomy was performed, and for rectal cancer, total mesorectal excision was conducted. Partial organ resection procedures were conducted as necessary, and specimens were collected and sent to the pathology department to ascertain the status of the surgical margins. Two pathologists examined the specimens and evaluated the treatment response. In the event of a discrepancy between the evaluations of the two pathologists, we consulted a third pathologist to resolve the differences. The tumor response following CCRT was assessed according to the American Joint Committee on Cancer system[18]. A circumferential resection margin (CRM) of < 1 mm was considered to be a positive margin. We defined pCR as the

absence of any malignant cells in a specimen, including the primary tumor and lymph nodes (ypT0N0).

Postoperative chemotherapy

Adjuvant chemotherapy (6 mo perioperative treatment) was suggested for patients with one of the following pathological parameters: Pathologic nodal metastases, positive resection margins, or pathologic T3-T4 tumors. An additional six cycles of adjuvant chemotherapy with FOLFOX were administered.

Toxicity evaluation and follow-up

Toxicity was evaluated at each weekly visit, and postoperative follow-up was conducted at 3-mo intervals. Acute adverse events were recorded in accordance with the Common Terminology Criteria for Adverse Events, version 4.2.

Statistical analysis

Categorical variables are presented as percentages, and continuous variables are presented as median values and ranges. Categorical variables were compared using the χ^2 test or Fisher's exact test. We applied kappa statistics to quantify and confirm interobserver agreement. A multivariate logistic regression model was used to identify independent predictive factors for pCR.

Follow-up and survival periods were measured from the surgery date to the end points. The Kaplan-Meier method was used to estimate DFS and OS, and the log-rank test was used to measure differences between the groups. A multivariate Cox proportional hazards model was used to analyze the associated clinicopathologic factors. All statistical analyses were performed using JMP software (version 9.0, SAS Institute Inc., Cary, NC, United States).

RESULTS

Table 1 presents the characteristics of the patients. The sigmoid colon was the most common site of colon cancer (n = 14), followed by the ascending colon (n = 7), cecum (n = 2), and transverse colon (n = 2). The irradiation treatment modalities included three-dimensional conformal radiotherapy (n = 15), volumetric arc therapy (n = 49), and tomotherapy (n = 24). According to imaging studies, the following adjacent organs were involved: The bladder (n = 13), uterus (n = 9), vagina (n = 6), small intestine (n = 8), prostate (n = 5), ureter (n = 2), stomach (n = 1), and perineum (n = 1). After reviewing each surgical specimen, we determined that the bladder of three patients, the uterus of one patient, and the stomach of one patient were pathologically involved. In the remaining cases, dead tumor cells and fibrosis were found within the resected or biopsied adjacent organs.

Acute toxicity and treatment compliance

Acute adverse events differed between the two chemotherapy groups. Overall, leukopenia (11.1%) was the most common grade 3 toxicity in the FOLFOX group, and diarrhea (14.2%) was the most common grade 3 toxicity in the capecitabine group. No grade 4 toxicity or treatment-related death was observed in the study participants.

All patients completed the suggested radiation dose. RT was interrupted for 1 wk because of grade 3 diarrhea (n = 2) in the FOLFOX group. In the FOLFOX group, three patients discontinued chemotherapy because of neutropenic fever (n = 2) and severe diarrhea (n = 1); no chemotherapy interruption occurred in the capecitabine group.

Surgical and pathological responses

In this study, two patients did not undergo radical resection after completing CCRT. One patient was diagnosed as having sigmoid colon cancer invading the uterus and left ureter; therefore, the patient did not receive radical resection because tumor fixation to the common iliac artery was found during the operation. The patient continued chemotherapy with FOLFOX followed by FOLFIRI and exhibited a stable disease at the 18-month follow-up (the last follow-up). The other patient with ascending colon cancer developed peritoneal carcinomatosis after completing CCRT. Therefore, two cycles of FOLFIRI were administered, but the patient died of tumor progression 7 mo after diagnosis.

Table 2 lists the patients' pathological results and tumor responses. For the 86 patients who underwent surgery, the pCR rate was 14%, and the R0 resection rate was

Table 1 Patient and treatment characteristics (*n* = 88), *n* (%)

Characteristic	*n* = 88
Age, median (yr, range)	63 (34-93)
Sex	
Male	42 (47.7)
Female	46 (52.3)
Location	
Colon	25 (28.4)
Rectum	63 (71.6)
cT stage	
T4a	44 (50)
T4b	44 (50)
cN stage	
N0	7 (8)
N1	37 (42)
N2	44 (50)
cTNM stage	
II	6 (6.8)
III	82 (93.2)
Tumor grade	
Well differentiated	4 (4.6)
Moderately differentiated	72 (81.8)
Poorly differentiated	12 (13.6)
Pretreatment CEA (ng/mL)	
≤ 5	46 (52.3)
> 5	42 (47.7)
Preoperative chemotherapy	
FOLFOX	75 (85.2)
Capecitabine	13 (14.8)
Radiation technique	
Tomotherapy	24 (27.9)
Volumetric arc therapy	49 (57)
Conformal radiotherapy	15 (15.1)
Radiation dose (Gy)	
< 50	26 (29.5)
≥ 50	62 (70.5)
Radiation-surgery interval (wk, range)	9 (5-40)

CEA: Carcinoembryonic antigen.

91.9%. Of the 61 patients with rectal cancer, 7 (11.5%) achieved pCR and 5 (8.2%) had positive CRMs. Of the 25 patients with colon cancer, 5 (20%) achieved pCR and 2 (8%) had positive CRMs. The κ value was 0.97, indicating excellent interobserver agreement in this study.

Table 3 presents a summary of the results of the univariate and multivariate analyses of clinical parameters used for pCR prediction. The univariate analysis

Table 2 Pathological results and tumor response to neoadjuvant treatment (*n* = 86)[1]

	***n* (%)**
ypT	
0	13 (15)
1	3 (3.8)
2	12 (13.8)
3	46 (53.4)
4	12 (14)
ypN	
0	72 (83.8)
1	10 (11.6)
2	4 (4.6)
Median number of resected nodes[2]	9 (2-26)
Median number of involved nodes[2]	0 (0-8)
Lymphovascular invasion	
Positive	15 (17.4)
Negative	71 (82.6)
Perineural invasion	
Positive	22 (25.5)
Negative	64 (74.5)
Resection margin	
Positive	7 (8.1)
Negative	79 (91.9)
Pathologic complete response	
Yes	12 (14)
No	74 (86)
Tumor regression grade	
0	13 (15.1)
1	30 (34.9)
2	27 (31.4)
3	16 (18.6)
Pathologic T stage	
Downstaging	74 (86)
Stable	112 (14)
Progressive	0 (0)
Pathologic N stage	
Downstaging	75 (87.3)
Stable	7 (8.1)
Progressive	4 (4.6)

[1]Two patients (T4bN2M0 and T4aN2M0) did not undergo surgical resection.
[2]Median (range).

indicated that FOLFOX-based CCRT was significantly associated with pCR occurrence (P = 0.037) and that a long radiation-surgery interval tended to improve pCR (P = 0.074). The multivariate analysis revealed that receiving the FOLFOX regimen was an independent predictor of pCR (odds ratio, 4.755; 95%CI, 2.118-88.203; P = 0.046).

Table 4 lists tumor and nodal responses to neoadjuvant CCRT for each patient. Among all patients with cT4a CRC, 7 (8.1%) achieved pCR and 15 (17.4%) had tumor downstaging to ypT0-2. Moreover, among all patients with T4b disease, 6 (7%) achieved pCR and 13 (15.1%) had ypT0-2 after neoadjuvant CCRT. When all clinical factors were included in the analysis, the FOLFOX plus RT group had a higher number of patients with tumor downstaging to ypT0-2 than the capecitabine-based CCRT group (34.9% *vs* 7.1%; P = 0.022). Of the 42 patients with T4b disease, 13 underwent multivisceral resection and the remaining 29 underwent radical resection with the preservation of surrounding organs.

Postoperative complications

No mortality was observed within 30 d after surgery. Two patients developed a wound abscess. One patient developed an intra-abdominal infection due to anastomotic leakage 1 mo after right hemicolectomy. Furthermore, three patients required surgical interventions because of adhesion ileus. Two patients developed rectovaginal fistulas. Of the 86 patients, 8 developed postoperative complications requiring intensive medical or surgical interventions (10.4%).

Survival data and failure patterns

The median follow-up time was 47 mo (range, 17-120 mo). At the time of analysis, 37 patients had died. The estimated 5-year OS and DFS rates were 70.8% and 61.4%, respectively (Figure 1A and B). Table 5 presents the results of univariate and multivariate analyses for prognostic parameters used to predict DFS and OS rates. The multivariate analysis revealed that resection margin [hazard ratio (HR), 3.120; P = 0.014], ypN stage (HR, 3.549; P = 0.042), and pathological response (HR, 2.560; P = 0.017) were independent factors associated with DFS; moreover, resection margin (HR, 4.136; P = 0.001) and pathological response (HR, 2.977; P = 0.003) were independent factors associated with OS. The Kaplan-Meier method revealed that the number of patients with negative resection margins was significantly higher than that of those with involved resection margins (P < 0.001 and P = 0.012, respectively; Figure 2A and B). In addition, patients who achieved pCR had higher DFS and OS rates than those who did not (P = 0.043 and P = 0.032, respectively; Figure 2C and D).

The failure patterns, according to the tumor location and clinical tumor stage, are summarized in Table 6. For patients with rectal cancer, cT4b disease resulted in a recurrence rate of 32.3%, which was higher than that (26.6%) among patients with cT4a disease. Among the patients with colon cancer, the recurrence rates in patients with cT4b and cT4a were 38.5% and 25%, respectively. A total of 19 patients (22.1%) developed distant metastases: The lung was the most common first site of distant metastasis (n = 9), followed by the liver (n = 5), bone (n = 2), para-aortic lymph nodes (n = 2), and peritoneal carcinomatosis (n = 1). Local recurrence was observed in 13 patients (15.1%). Only one patient with pCR developed peritoneal carcinomatosis and bone metastases 11 mo after surgery; she died of tumor progression 2 mo after developing distant metastases. No patient experienced local failure in the pCR group.

DISCUSSION

In general, cT4 CRC requires MVR to improve local control and survival. However, several studies have demonstrated that MVR leads to considerably high morbidity and mortality rates[3,19,20]. Therefore, in a population-based study of patients selected from the SEER registry, only 33.3% of 8380 patients with locally advanced adherent T4 CRC eventually underwent MVR, and the delivery of neoadjuvant RT was associated with decreased cases of MVR[21]. Accordingly, we evaluated the oncologic outcomes of patients with T4 CRC undergoing neoadjuvant CCRT and subsequent surgery.

Neoadjuvant CCRT followed by surgical resection is the main treatment for LARC[8,9]. To enhance the effects of CCRT in tumor downsizing, oxaliplatin is added to the fluoropyrimidine-based regimen during RT. Several phase III randomized trials have failed to demonstrate the superiority of the oxaliplatin-based regimen over fluoropyrimidine-based therapy, with only the German CAO/ARO/AIO-04 trial demonstrating a positive impact of FOLFOX-based CCRT on pCR[22-24]. However, some studies have extended the delivery of FOLFOX after CCRT and revealed that

Table 3 Univariate and multivariate analyses for clinical parameters used to predict pCR

Variable	Univariate	Multivariate	
	P value	OR (95%CI)	*P* value
Age (< 60 yr *vs* ≥ 60 yr)	0.471	0.556 (0.096-2.609)	0.464
Sex (female *vs* male)	0.416	1.722 (0.327-9.531)	0.515
Location (colon *vs* rectum)	0.107	2.615 (0.498-14.826)	0.251
cT stage (T4a *vs* T4b)	0.247	1.221 (0.218-7.667)	0.821
cN stage (N0 *vs* N+)	0.152	0.415 (0.104-1.337)	0.145
Tumor grade (WD/MD *vs* PD)	0.509	3.071 (0.341-70.370)	0.337
CEA (≤ 5 *vs* > 5)	0.894	0.611 (0.106-3.136)	0.556
Neoadjuvant chemotherapy (FOLFOX *vs* capecitabine)	0.037[a]	4.755 (2.118-88.203)	0.046[a]
Radiation dose (< 50 Gy *vs* ≥ 50 Gy)	0.265	0.507 (0.058-3.187)	0.478
Radiation-surgery interval (≤ 9 wk *vs* > 9 wk)	0.074	0.836 (0.013-3.061)	0.107

[a]$P < 0.05$.

CEA: Carcinoembryonic antigen; MD: Moderately differentiated; pCR: Pathological complete response; PD: Poorly differentiated; WD: Well differentiated.

Table 4 Comparison of clinical staging with pathologic T and N staging (*n* = 86)[1]

Clinical staging	Pathologic T staging						ypN negative	ypN positive	Total
	ypT0	ypT1	ypT2	ypT3	ypT4a	ypT4b			
cT4a	7 (8.1)	3 (3.5)	5 (5.8)	24 (27.9)	3 (3.5)	2 (2.3)			44 (51.2)
cT4b	6 (7)	0 (0)	7 (8.1)	22 (25.6)	4 (4.6)	3 (3.5)			42 (48.8)
cN negative							6 (7)	1 (1.1)	7 (8.1)
cN positive							66 (76.8)	13 (15.1)	79 (91.9)
Total	13 (15.1)	3 (3.5)	12 (13.9)	46 (53.5)	7 (8.1)	5 (5.8)	72 (83.8)	14 (16.2)	86 (100)

c: Clinical (in this case evaluated by imaging); ypT: Pathologic T-stage posttreatment; ypN: Pathologic N-stage posttreatment.

[1]Two patients (T4bN2M0 and T4aN2M0) did not undergo surgical resection.

extending the oxaliplatin regimen resulted in higher rates of pCR and major regression compared with the delivery of FOLFOX only during RT (as done in the aforementioned phase III trials)[25,26]. To summarize, despite the disappointing results of concurrently administering oxaliplatin during RT, some studies have demonstrated that implementing a more intense neoadjuvant chemotherapy regimen either before radiation[27,28] or concurrently with radiation[29,30] or extending administration of chemotherapy to the resting period between RT and surgery[31-33] resulted in improved oncological outcomes. In our study, we delivered FOLFOX prior to, concurrently with, and following RT for most patients with cT4 CRC (86%) in an attempt to maximize the effects of CCRT on tumor regression for those with locally advanced adherent CRC. The remaining patients with cT4 disease received capecitabine only during RT because the neoadjuvant FOLFOX regimen plus RT was unavailable at that time.

Radiation-induced tumor regression is time dependent[17,31]. In this study, a long interval between radiation and surgery tended to be associated with high pCR rates ($P = 0.074$), possibly because we included only locally advanced T4 CRC for analysis; advanced tumors require high-intensity treatment. Garcia *et al*[26] reported that adding cycles of mFOLFOX6 during the radiation-surgery interval and prolonging the interval between radiation and surgery could increase pCR rates. Liang *et al*[34] observed that the addition of chemotherapy during the resting period, with a long interval between radiation and surgery, resulted in improved pCR and DFS rates compared with the nonaddition of consolidation chemotherapy.

The pCR rate in the current study was 14%, which is lower than those reported in other studies[23-26]. For rectal cancer treatment, neoadjuvant CCRT resulted in varying

Table 5 Univariate and multivariate analyses for clinical parameters used to predict disease-free survival and overall survival

Variable	Disease-free survival			Overall survival		
	Univariate *P* value	Multivariate		Univariate *P* value	Multivariate	
		HR (95%CI)	*P* value		HR (95%CI)	*P* value
Age (< 60 *vs* ≥ 60 yrs)	0.492	0.770 (0.255-1.618)	0.492	0.729	0.621 (0.314-1.245)	0.177
Sex (female *vs* male)	0.493	0.773 (0.375-1.626)	0.493	0.678	0.906 (0.442-1.812)	0.783
Location (colon *vs* rectum)	0.353	0.216 (0.102-1.231)	0.153	0.346	0.291 (0.054-1.154)	0.082
cT stage (T4a *vs* T4b)	0.127	2.423 (0.604-9.836)	0.258	0.206	2.611 (0.752-9.054)	0.128
cN stage (N0 *vs* N+)	0.127	0.690 (0.139-3.014)	0.157	0.102	0.336 (0.094-1.087)	0.078
Tumor grade (WD/MD *vs* PD)	0.335	0.503 (0.098-1.936)	0.413	0.423	0.840 (0.247-2.500)	0.765
CEA (≤ 5 ng/mL *vs* > 5 ng/mL)	0.418	1.422 (0.614-3.391)	0.383	0.528	1.219 (0.581-2.622)	0.602
Neoadjuvant chemotherapy (FOLFOX *vs* Capecitabine)	0.142	3.549 (0.944-7.467)	0.082	0.117	2.846 (0.860-8.715)	0.158
Radiation dose (< 50 Gy *vs* ≥ 50 Gy)	0.351	0.291 (0.054-1.154)	0.182	0.327	2.525 (0.347-5.843)	0.221
Radiation-surgery interval (≤ 9 wk *vs* > 9 wk)	0.086	1.236 (0.792-5.276)	0.097	0.106	2.064 (0.589-7.062)	0.167
ypT stage (ypT3-4 *vs* ypT0-2)	0.237	2.484 (0.744-5.691)	0.636	0.097	2.150 (0.820-6.123)	0.121
ypN stage (ypN+ *vs* ypN0)	0.005	3.120 (1.245-8.357)	0.017[a]	0.073	1.771 (0.435-6.255)	0.405
Lymphovascular invasion (positive *vs* negative)	0.363	2.503 (0.724-7.788)	0.141	0.175	3.046 (0.961-9.081)	0.069
Perineural invasion (positive *vs* negative)	0.072	2.649 (0.869-8.976)	0.087	0.091	1.222 (0.323-4.078)	0.757
Resection margin (positive *vs* negative)	0.001	3.549 (1.004-12.747)	0.014[a]	0.013	4.136 (1.675-10.829)	0.001[a]
Pathological response (non-pCR *vs* pCR)	0.045	2.560 (1.186-6.013)	0.042[a]	0.031	2.977 (1.420-6.369)	0.003[a]

[a]*P* < 0.05.

CEA: Carcinoembryonic antigen; MD: Moderately differentiated; pCR: Pathological complete response; PD: Poorly differentiated; WD: Well differentiated.

Table 6 Failure patterns according to tumor location and clinical tumor stage

Recurrence	Colon		Rectum	
	cT4a (%)	cT4b (%)	cT4a (%)	cT4b (%)
Local/regional only	2 (16.7)	1 (7.7)	1 (3.3)	3 (9.7)
Distant only	1 (8.3)	2 (15.4)	5 (16.7)	5 (16.1)
Local/regional/distant	0 (0)	2 (15.4)	2 (6.6)	2 (6.5)
No recurrence	9 (75)	8 (61.5)	22 (73.4)	21 (67.7)
Total	12 (100)	13 (100)	30 (100)	31 (100)

pCR rates, ranging from 13% to 38%[9,27-29]. Numerous clinical predictors of pCR have been identified, and advanced clinical T stage has been associated with a relatively low pCR rate[15-17]. Because our study focused on T4 disease, we expected to observe a relatively low pCR rate.

MVR has a high R0 resection rate for patients with locally advanced T4 CRC[19,21,35]. Such aggressive surgery yields improved outcomes, but at the cost of increases in postoperative morbidity and mortality rates. Studies have reported such surgery to be associated with morbidity rates of 11%-49% and mortality rates of 0%-9%[19-21,35]. The tumor downstaging of T4 disease facilitates complete tumor resection; this may thus prevent complications of MVR. In our study, only 13 of 42 patients (31%) with cT4b disease required MVR after neoadjuvant CCRT. Qiu *et al*[36] revealed that MVR was required in only seven patients (33.3%) with locally advanced colon cancer. Therefore, neoadjuvant CCRT could diminish tumor infiltration and the necessity of MVR, which

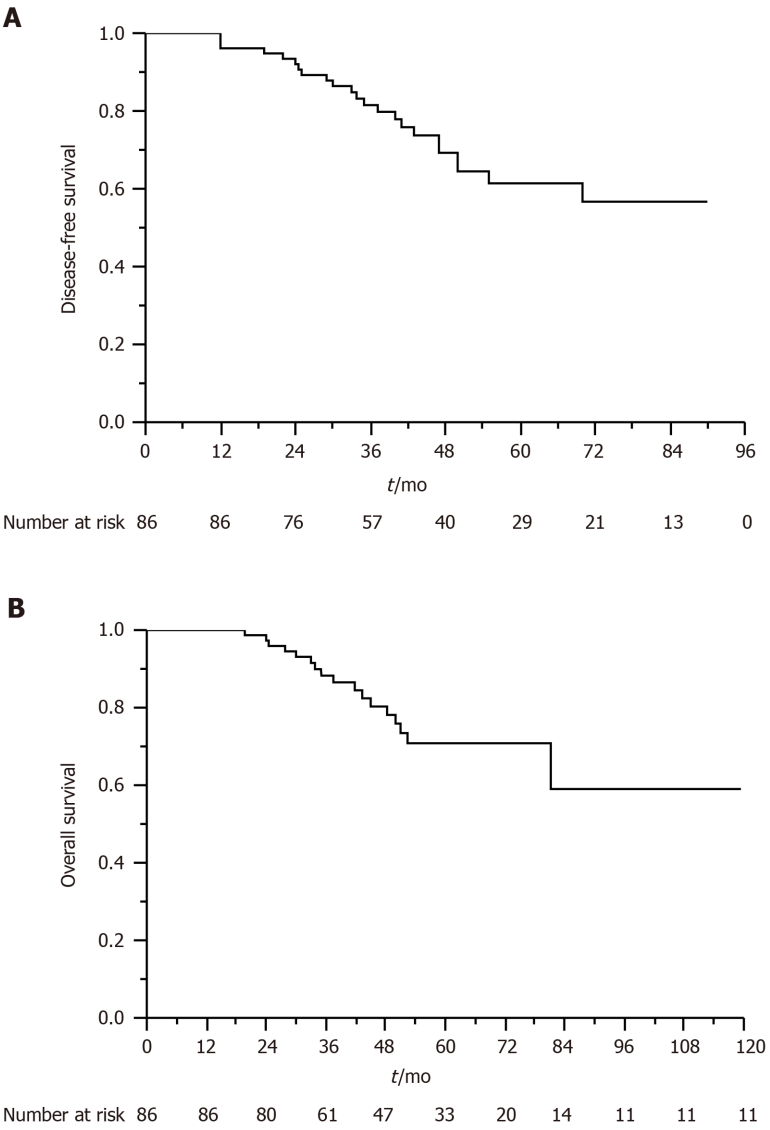


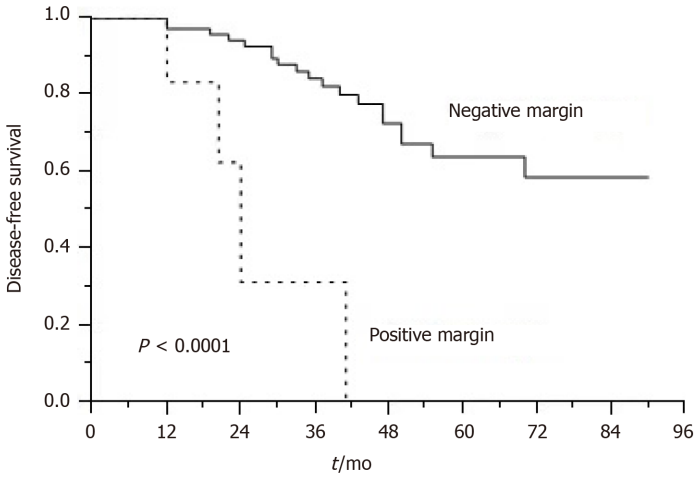
Figure 1 Disease-free survival and overall survival in patients with T4 colorectal cancer undergoing neoadjuvant chemoradiation therapy followed by radical resection.

may subsequently reduce the occurrence of postoperative complications.

The response to neoadjuvant CCRT varies among patients. Numerous studies have reported that patients who achieve pCR tend to exhibit excellent tumor control and survival[13,32,37]. Therefore, many researchers have identified some predictors of pCR, including cT3/4 and N+[15,17,32]. However, few studies have evaluated the response of cT4 CRC to CCRT or the predictors of pCR in patients with cT4 CRC undergoing neoadjuvant CCRT. In the current study, patients who underwent an intensified neoadjuvant therapy and received the FOLFOX regimen before, during, and after RT had higher chances of achieving pCR than those who received capecitabine-based CCRT. The Chinese FOWARC trial demonstrated that mFOLFOX6-based preoperative CCRT had a higher pCR rate than fluorouracil-based treatment[25]. Our preoperative intensified regimen was similar to the regimens used in the Chinese FOWARC study[33]. Therefore, our results seem to accord with the Chinese FOWARC study.

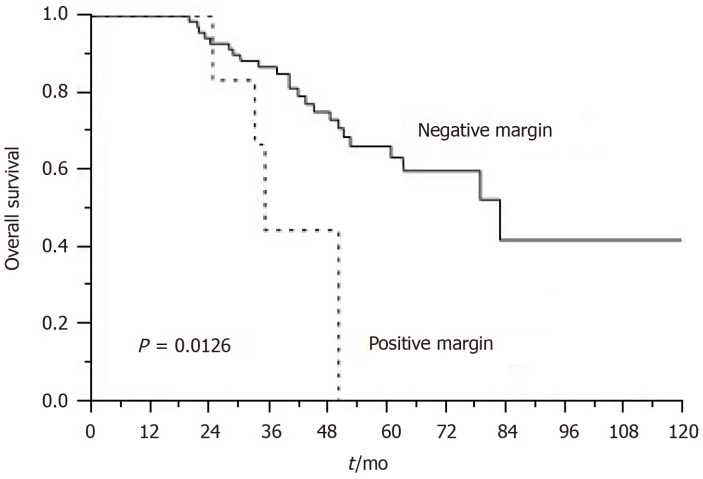
The current study revealed that R0 resection was associated with favorable DFS and OS, which accords with the results of other studies[3,6]. R0 resection rates have been reported to range from 40% to 100% in patients with locally advanced T4 CRC who underwent radical resection with or without neoadjuvant therapy[10,35,36]. Cukier *et al*[10] analyzed 33 patients, all of whom underwent R0 resection after CCRT, with locally adherent colon cancer patients who received neoadjuvant CCRT and MVR. Qiu *et al*[36] studied 21 patients with locally advanced sigmoid colon cancer who underwent preoperative CCRT followed by surgery, and they observed an R0 resection rate of 95.2%. The published R0 resection rates (generally > 90%) in patients who underwent

A



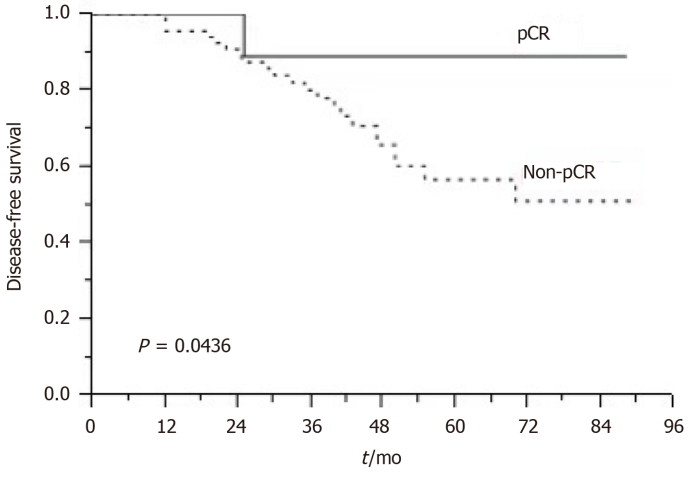
Number at risk									
Negative	79	79	69	51	36	26	18	12	0
Positive	7	7	3	2	0	0	0	0	0

B



Number at risk											
Negative	79	79	78	59	44	32	20	13	9	9	9
Positive	7	7	7	6	3	0	0	0	0	0	0

C



Number at risk									
Non-pCR	74	74	61	47	35	23	16	10	0
pCR	12	12	11	7	6	5	4	4	0

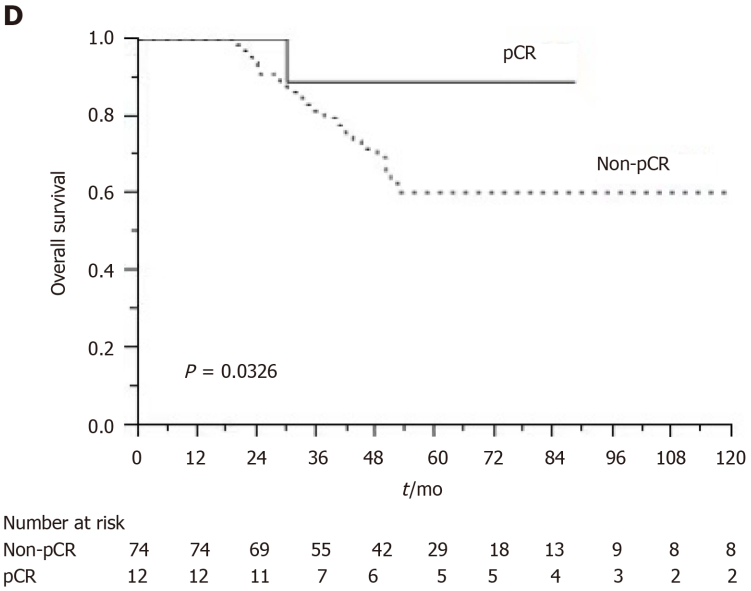


Figure 2 Disease-free survival and overall survival in patients with a negative surgical margin *vs* those with an involved surgical margin and in patients with pathological complete response *vs* those without. pCR: Pathological complete response.

CCRT followed by surgery were higher than those in patients who underwent surgery first (range: 40%-90%).

The benefits of neoadjuvant CCRT for locally advanced colon cancer remain controversial. Two single-arm cohort studies have evaluated the role of neoadjuvant CCRT in locally advanced colon cancer, and both studies have reported high R0 resection rates (100% and 95.2%, respectively)[10,36]. Zhou *et al*[12] compared the oncological results of patients (n = 58) with locally advanced colon cancer who underwent neoadjuvant FOLFOX-based CCRT followed by surgery with those of patients (n = 44) with the same disease who received surgery without neoadjuvant CCRT; they determined that neoadjuvant CCRT improved the pCR and resection rates, in addition to improving 3-year DFS rates.

We acknowledge some limitations of the current study. First, the sample size was relatively small, and the follow-up time was short. Consequently, long-term oncological outcomes and adverse events could not be adequately investigated. Second, this was a retrospective study; therefore, selection bias was possible. Third, chemotherapeutic regimens, radiation doses, and radiation techniques were not identical among all enrolled patients.

CONCLUSION

Neoadjuvant CCRT results in high pCR and complete resection rates for patients with T4 CRC. The aggressive approach involving the administration of the FOLFOX regimen before, during, and after RT proves to be safe and capable of improving pCR in patients with cT4 CRC. Negative resection margins and pCR are significantly associated with survival. Further prospective randomized studies are warranted to validate our results.

ARTICLE HIGHLIGHTS

Research background

Patients diagnosed with clinical T4 colorectal cancer are at high risk of recurrence because of difficulty in achieving free surgical margins. Multi-visceral resection is needed for the complete resection of the disease.

Research motivation

Patients diagnosed with clinical T4 colorectal cancer are at high risk of recurrence

because of difficulty in achieving free surgical margins. Multi-visceral resection is needed for the complete resection of the disease.

Research objectives

Patients diagnosed with clinical T4 colorectal cancer are at high risk of recurrence because of difficulty in achieving free surgical margins. Multi-visceral resection is needed for the complete resection of the disease.

Research methods

We retrospectively reviewed colorectal cancer (CRC) patients from the database of The Kaohsiung Medical University Hospital from August 2010 to September 2018. Eighty-six patients who completed neoadjuvant chemoradiation and radical resection were enrolled for analysis. The neoadjuvant regimens in this study were capecitabine plus radiotherapy, and FOLFOX plus radiotherapy. The radiation dose was 45 to 50.4 Gy with a daily fraction of 1.8 or 2 Gy. We used multivariate logistic regression analysis to identify independent predictors of pathological complete response (pCR). Using Kaplan-Meier method and log-rank test, we measured the disease-free survival (DFS) and overall survival (OS) between groups, where multivariate Cox proportional hazard models were used to analyze the impact of pCR and resection margins as prognostic factors.

Research results

The rates of pCR and R0 resection were 14% and 91.9%, respectively. Nineteen patients (22.1%) developed distant metastases and local recurrence was found in 13 patients (15.1%). Patients who underwent FOLFOX plus radiotherapy were more likely to achieve pCR compared to those who received capecitabine plus radiotherapy (P = 0.046). Multivariate analysis revealed that an R0 resection was associated with favorable DFS (P = 0.014) and OS (P = 0.001), and the pCR group obtained better DFS (P = 0.042) and OS (P = 0.003) than the non-pCR group.

Research conclusions

Neoadjuvant chemoradiation results in high rates of pCR and complete resection for patients with T4 CRC. R0 resection and pCR are significant predictors of favorable survival.

Research perspectives

Neoadjuvant chemoradiation should be considered as one of the treatment options in T4 colon and rectal cancer. Further prospective randomized studies are warranted to validate our results.

REFERENCES

1 **Siegel R**, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA Cancer J Clin* 2014; **64**: 104-117 [PMID: 24639052 DOI: 10.3322/caac.21220]

2 **Ministry of Health and Welfare**, the Executive Yuan, Republic of China. Health and Vital Statistics. Available from: http://www.mohw.gov.tw/CHT/Ministry/

3 **Lehnert T**, Methner M, Pollok A, Schaible A, Hinz U, Herfarth C. Multivisceral resection for locally advanced primary colon and rectal cancer: an analysis of prognostic factors in 201 patients. *Ann Surg* 2002; **235**: 217-225 [PMID: 11807361 DOI: 10.1097/00000658-200202000-00009]

4 **Govindarajan A**, Fraser N, Cranford V, Wirtzfeld D, Gallinger S, Law CH, Smith AJ, Gagliardi AR. Predictors of multivisceral resection in patients with locally advanced colorectal cancer. *Ann Surg Oncol* 2008; **15**: 1923-1930 [PMID: 18473145 DOI: 10.1245/s10434-008-9930-1]

5 **Ueno H**, Mochizuki H, Akagi Y, Kusumi T, Yamada K, Ikegami M, Kawachi H, Kameoka S, Ohkura Y, Masaki T, Kushima R, Takahashi K, Ajioka Y, Hase K, Ochiai A, Wada R, Iwaya K, Shimazaki H, Nakamura T, Sugihara K. Optimal colorectal cancer staging criteria in TNM classification. *J Clin Oncol* 2012; **30**: 1519-1526 [PMID: 22430272 DOI: 10.1200/JCO.2011.39.4692]

6 **Croner RS**, Merkel S, Papadopoulos T, Schellerer V, Hohenberger W, Goehl J. Multivisceral resection for colon carcinoma. *Dis Colon Rectum* 2009; **52**: 1381-1386 [PMID: 19617748 DOI: 10.1007/DCR.0b013e3181ab580b]

7 **Gebhardt C**, Meyer W, Ruckriegel S, Meier U. Multivisceral resection of advanced colorectal carcinoma. *Langenbecks Arch Surg* 1999; **384**: 194-199 [PMID: 10328174 DOI: 10.1007/s004230050191]

8 **Sauer R**, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R; German Rectal Cancer Study

Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**: 1731-1740 [PMID: 15496622 DOI: 10.1056/NEJMoa040694]

9 **Roh MS**, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, Kahlenberg MS, Baez-Diaz L, Ursiny CS, Petrelli NJ, Wolmark N. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol* 2009; **27**: 5124-5130 [PMID: 19770376 DOI: 10.1200/JCO.2009.22.0467]

10 **Cukier M**, Smith AJ, Milot L, Chu W, Chung H, Fenech D, Herschorn S, Ko Y, Rowsell C, Soliman H, Ung YC, Wong CS. Neoadjuvant chemoradiotherapy and multivisceral resection for primary locally advanced adherent colon cancer: a single institution experience. *Eur J Surg Oncol* 2012; **38**: 677-682 [PMID: 22632848 DOI: 10.1016/j.ejso.2012.05.001]

11 **Huang CM**, Huang MY, Ma CJ, Yeh Y-, Tsai HL, Huang CW, Huang CJ, Wang JY. Neoadjuvant FOLFOX chemotherapy combined with radiotherapy followed by radical resection in patients with locally advanced colon cancer. *Radiat Oncol* 2017; **12**: 48 [PMID: 28270172 DOI: 10.1186/s13014-017-0790-3]

12 **Zhou J**, Guo Z, Yu W, Li S, Qiao W. Clinical Evaluation of Preoperative Radiotherapy Combined with FOLFOX Chemotherapy on Patients with Locally Advanced Colon Cancer. *Am Surg* 2019; **85**: 313-320 [PMID: 31043188]

13 **Rödel C**, Martus P, Papadoupolos T, Füzesi L, Klimpfinger M, Fietkau R, Liersch T, Hohenberger W, Raab R, Sauer R, Wittekind C. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 2005; **23**: 8688-8696 [PMID: 16246976 DOI: 10.1200/jco.2005.02.1329]

14 **Theodoropoulos G**, Wise WE, Padmanabhan A, Kerner BA, Taylor CW, Aguilar PS, Khanduja KS. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. *Dis Colon Rectum* 2002; **45**: 895-903 [PMID: 12130878 DOI: 10.1007/s10350-004-6325-7]

15 **Huh JW**, Kim HR, Kim YJ. Clinical prediction of pathological complete response after preoperative chemoradiotherapy for rectal cancer. *Dis Colon Rectum* 2013; **56**: 698-703 [PMID: 23652742 DOI: 10.1097/DCR.0b013e3182837e5b]

16 **Peng H**, Wang C, Xiao W, Lin X, You K, Dong J, Wang Z, Yu X, Zeng Z, Zhou T, Gao Y, Wen B. Analysis of Clinical characteristics to predict pathologic complete response for patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. *J Cancer* 2018; **9**: 2687-2692 [PMID: 30087709 DOI: 10.7150/jca.25493]

17 **Al-Sukhni E**, Attwood K, Mattson DM, Gabriel E, Nurkin SJ. Predictors of Pathologic Complete Response Following Neoadjuvant Chemoradiotherapy for Rectal Cancer. *Ann Surg Oncol* 2016; **23**: 1177-1186 [PMID: 26668083 DOI: 10.1245/s10434-015-5017-y]

18 **Mace AG**, Pai RK, Stocchi L, Kalady MF. American Joint Committee on Cancer and College of American Pathologists regression grade: a new prognostic factor in rectal cancer. *Dis Colon Rectum* 2015; **58**: 32-44 [PMID: 25489692 DOI: 10.1097/DCR.0000000000000266]

19 **Park S**, Lee YS. Analysis of the prognostic effectiveness of a multivisceral resection for locally advanced colorectal cancer. *J Korean Soc Coloproctol* 2011; **27**: 21-26 [PMID: 21431093 DOI: 10.3393/jksc.2011.27.1.21]

20 **Nakafusa Y**, Tanaka T, Tanaka M, Kitajima Y, Sato S, Miyazaki K. Comparison of multivisceral resection and standard operation for locally advanced colorectal cancer: analysis of prognostic factors for short-term and long-term outcome. *Dis Colon Rectum* 2004; **47**: 2055-2063 [PMID: 15657654 DOI: 10.1007/s10350-004-0716-7]

21 **Govindarajan A**, Coburn NG, Kiss A, Rabeneck L, Smith AJ, Law CH. Population-based assessment of the surgical management of locally advanced colorectal cancer. *J Natl Cancer Inst* 2006; **98**: 1474-1481 [PMID: 17047196 DOI: 10.1093/jnci/djj396]

22 **Aschele C**, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, Artale S, Tagliagambe A, Ambrosini G, Rosetti P, Bonetti A, Negru ME, Tronconi MC, Luppi G, Silvano G, Corsi DC, Bochicchio AM, Chiaulon G, Gallo M, Boni L. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol* 2011; **29**: 2773-2780 [PMID: 21606427 DOI: 10.1200/JCO.2010.34.4911]

23 **Gérard JP**, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, Vendrely V, François E, de La Roche G, Bouché O, Mirabel X, Denis B, Mineur L, Berdah JF, Mahé MA, Bécouarn Y, Dupuis O, Lledo G, Montoto-Grillot C, Conroy T. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010; **28**: 1638-1644 [PMID: 20194850 DOI: 10.1200/JCO.2009.25.8376]

24 **O'Connell MJ**, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, Pitot HC, Shields AF, Landry JC, Ryan DP, Parda DS, Mohiuddin M, Arora A, Evans LS, Bahary N, Soori GS, Eakle J, Robertson JM, Moore DF Jr, Mullane MR, Marchello BT, Ward PJ, Wozniak TF, Roh MS, Yothers G, Wolmark N. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. *J Clin Oncol* 2014; **32**: 1927-1934 [PMID: 24799484 DOI: 10.1200/JCO.2013.53.7753]

25 **Deng Y**, Chi P, Lan P, Wang L, Chen W, Cui L, Chen D, Cao J, Wei H, Peng X, Huang Z, Cai G, Zhao R, Huang Z, Xu L, Zhou H, Wei Y, Zhang H, Zheng J, Huang Y, Zhou Z, Cai Y, Kang L, Huang M, Peng J, Ren D, Wang J. Modified FOLFOX6 With or Without Radiation Versus

Fluorouracil and Leucovorin With Radiation in Neoadjuvant Treatment of Locally Advanced Rectal Cancer: Initial Results of the Chinese FOWARC Multicenter, Open-Label, Randomized Three-Arm Phase III Trial. *J Clin Oncol* 2016; **34**: 3300-3307 [PMID: 27480145 DOI: 10.1200/JCO.2016.66.6198]

26 **Garcia-Aguilar J**, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, Kumar AS, Oommen S, Coutsoftides T, Hunt SR, Stamos MJ, Ternent CA, Herzig DO, Fichera A, Polite BN, Dietz DW, Patil S, Avila K; Timing of Rectal Cancer Response to Chemoradiation Consortium. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. *Lancet Oncol* 2015; **16**: 957-966 [PMID: 26187751 DOI: 10.1016/S1470-2045(15)00004-2]

27 **Chau I**, Brown G, Cunningham D, Tait D, Wotherspoon A, Norman AR, Tebbutt N, Hill M, Ross PJ, Massey A, Oates J. 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 [PMID: 16446339 DOI: 10.1200/jco.2005.04.4875]

28 **Fernández-Martos C**, Pericay C, Aparicio J, Salud A, Safont M, Massuti B, Vera R, Escudero P, Maurel J, Marcuello E, Mengual JL, Saigi E, Estevan R, Mira M, Polo S, Hernandez A, Gallen M, Arias F, Serra J, Alonso V. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. *J Clin Oncol* 2010; **28**: 859-865 [PMID: 20065174 DOI: 10.1200/JCO.2009.25.8541]

29 **Rödel C**, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, Graeven U, Arnold D, Lang-Welzenbach M, Raab HR, Sülberg H, Wittekind C, Potapov S, Staib L, Hess C, Weigang-Köhler K, Grabenbauer GG, Hoffmanns H, Lindemann F, Schlenska-Lange A, Folprecht G, Sauer R; German Rectal Cancer Study Group. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. *Lancet Oncol* 2012; **13**: 679-687 [PMID: 22627104 DOI: 10.1016/S1470-2045(12)70187-0]

30 **Bosset JF**, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Ollier JC; EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**: 1114-1123 [PMID: 16971718 DOI: 10.1056/NEJMoa060829]

31 **Garcia-Aguilar J**, Smith DD, Avila K, Bergsland EK, Chu P, Krieg RM; 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 [PMID: 21494121 DOI: 10.1097/SLA.0b013e3182196e1f]

32 **Habr-Gama A**, Perez RO, Sabbaga J, Nadalin W, São Julião GP, Gama-Rodrigues J. 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 [PMID: 19934911 DOI: 10.1007/DCR.0b013e3181ba14ed]

33 **Huang CM**, Huang MY, Tsai HL, Huang CW, Ma CJ, Yeh YS, Juo SH, Huang CJ, Wang JY. An observational study of extending FOLFOX chemotherapy, lengthening the interval between radiotherapy and surgery, and enhancing pathological complete response rates in rectal cancer patients following preoperative chemoradiotherapy. *Therap Adv Gastroenterol* 2016; **9**: 702-712 [PMID: 27582883 DOI: 10.1177/1756283X16656690]

34 **Liang HQ**, Dong ZY, Liu ZJ, Luo J, Zeng Q, Liao PY, Wu DH. Efficacy and safety of consolidation chemotherapy during the resting period in patients with local advanced rectal cancer. *Oncol Lett* 2019; **17**: 1655-1663 [PMID: 30675225 DOI: 10.3892/ol.2018.9804]

35 **Eveno C**, Lefevre JH, Svrcek M, Bennis M, Chafai N, Tiret E, Parc Y. Oncologic results after multivisceral resection of clinical T4 tumors. *Surgery* 2014; **156**: 669-675 [PMID: 24953279 DOI: 10.1016/j.surg.2014.03.040]

36 **Qiu B**, Ding PR, Cai L, Xiao WW, Zeng ZF, Chen G, Lu ZH, Li LR, Wu XJ, Mirimanoff RO, Pan ZZ, Xu RH, Gao YH. Outcomes of preoperative chemoradiotherapy followed by surgery in patients with unresectable locally advanced sigmoid colon cancer. *Chin J Cancer* 2016; **35**: 65 [PMID: 27389519 DOI: 10.1186/s40880-016-0126-y]

37 **Huang CM**, Huang CW, Ma CJ, Yeh YS, Su WC, Chang TK, Tsai HL, Juo SH, Huang MY, Wang JY. Predictive Value of FOLFOX-Based Regimen, Long Interval, Hemoglobin Levels and Clinical Negative Nodal Status, and Postchemoradiotherapy CEA Levels for Pathological Complete Response in Patients with Locally Advanced Rectal Cancer after Neoadjuvant Chemoradiotherapy. *J Oncol* 2020; **2020**: 9437684 [PMID: 32411245 DOI: 10.1155/2020/9437684]

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