Original Article

DOI: 10.5582/bst.2022.01432

2-4 weeks is the optimal time to operate on colorectal liver metastasis after neoadjuvant chemotherapy

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SUMMARY Neoadjuvant chemotherapy (NAC) is generally accepted for treatment of liver metastasis of colorectal cancer (CRLM), but what is a reasonable interval between the latest NAC and surgery is still unknown. The aim of the current study was to investigate the proper timing of surgery after NAC. Subjects were 141 patients with CRLM who underwent NAC and then surgery were retrospectively identified from 2008 to 2020. They were divided into a short interval group (SIG, ≤ 4 weeks) and long interval group (LIG, > 4 weeks) using the software X-tile. The SIG was subclassified group into 3 time periods (1-2 weeks, 2-3 weeks, and 3-4 weeks) to assess the incidence of complications. Patients in the SIG were more likely to have significantly better recurrence-free survival (RFS) (3-year RFS of 47.4% *vs*. 20.5%, $P = 0.043$) and no difference in overall survival (OS) (3-year OS 76.1% *vs*. 79.9%, $P = 0.635$). The postoperative complication rate was 23.5% in the SIG and 14.0% in the LIG ($P = 0.198$). The postoperative complication rate in the 1-2 weeks subgroup was marginally higher than that in the > 4 weeks subgroup (35% *vs.* 14.3% $P = 0.055$). Multivariate analysis revealed that chemotherapy-free intervals of 1-2 weeks were an independent predictor of increased postoperative complications (OR = 0.263, 95% CI 0.7-0.985 $P = 0.048$). Patients who underwent surgery within 4 weeks of NAC had better RFS. In addition, 1-2 weeks was an independent factor influencing the development of more complications. For patients with CRLM, performing surgery within 2-4weeks of NAC was feasible and safe, and it did not increase the incidence of postoperative complications but it did prolong RFS.

Keywords colorectal cancer, liver metastasis, neoadjuvant chemotherapy, chemotherapy-free interval

1. Introduction

Colorectal cancer (CRC) is the world's most common tumor of the digestive tract, with more than 550,000 deaths each year (*1,2*). The liver is the most frequent metastatic site of CRC and liver metastasis of colorectal cancer has a worse prognosis. Due to its anatomical characteristics, liver metastasis will be detected in up to 30-50% of patients as the disease progresses (*3,4*). Surgery plays a dominant role in radical therapy (*5*). However, about a quarter of people with CRLM are candidates for radical liver resection (*6*). For patients with resectable CRLM, NAC combined with surgical resection is increasingly being advocated and has been proven to prolong patients' recurrence-free survival (RFS) (*7,8*). Although NAC is recommended for those who were diagnosed with CRLM with a high clinical risk score (CRS) according to the guidelines of the Chinese Society of Clinical Oncology (CSCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO), a consensus on the proper interval between NAC and surgery has yet to be reached (*9-12*). Related studies have analyzed the effect of the interval length on efficacy. Sutton *et al*. (*13*) concluded that intervals longer than 2 months lead to worse RFS and OS. Chen *et al*. (*14*) in 2020 noted better oncology outcomes with intervals of less than 5 weeks. However, adverse effects of neoadjuvant chemotherapy (NAC) can worsen intraoperative bleeding, such as oxaliplatin-induced hepatic sinusoidal dilatation and irinotecan-induced fatty liver (*15,16).* Welsh *et al*. (*17*) found that patients who had liver resection within 4 weeks of NAC had the highest incidence of postoperative complications. A long duration of systemic therapy may promote the progression of disease. The most appropriate timing for surgery needs to be investigated.

2. Materials and Methods

2.1. Patient selection

Patients with CRLM who underwent hepatectomy after NAC between 2008 and 2020 at Zhejiang Cancer Hospital were retrospectively studied. All patients were confirmed to be potential candidates for resection before receiving NAC. Patients who had received preoperative radiotherapy or transcatheter arterial chemoembolization (TACE) or who had extrahepatic metastases or positive surgical margins were excluded. CRLM was verified by pathology and immunohistochemistry. The baseline characteristics, perioperative data, and NAC regimens were acquired from the electronic medical record system of Zhejiang Cancer Hospital. In compliance with the declaration of Helsinki, this study was conducted with the approval of the medical ethics committee of Zhejiang Cancer Hospital.

Surgery was selected for appropriate patients after NAC based on tumor resectability and the physical condition of the patient. The majority of patients underwent less than 6 cycles of NAC in this 3-month period. The regimens of NAC consisted of capecitabine, 5-fluorouracil, oxaliplatin, and irinotecan. Patients who received NAC along with bevacizumab all underwent surgery after stopping the drug for more than six weeks.

2.2. Procedure

For the patients who underwent liver and colorectal resection simultaneously, colon or rectal radical resection was performed by the surgeon of the department of colorectal surgery. A resection of less than 3 Couinaud segments was defined as minor liver resection; otherwise, it was defined as major liver resection. The low central venous pressure (CVP) technique was used to reduce intraoperative bleeding. The Pringle maneuver was use to block hepatic inflow, which was limited to 15 min, and the interval between blocking was more than 5 min. An ultrasonic scalpel was used to transect liver parenchyma.

2.3. Definitions

Multiple metastases refer to more than 1 lesion in the liver. RFS was defined as the period of time from surgery to the first diagnosis of tumor recurrence. OS was defined as the duration from surgery to the time of death or the last follow-up. The chemotherapy-free interval (CFI) was defined as the interval from the end of the last NAC to surgery. Postoperative complications included bleeding, liver-related complications, and infectious complications. Liver-related complications included a bile leak, ascites, or postoperative liver dysfunction (international normalized ratio (INR) elevated more than 1.8-fold the normal upper limit or total bilirubin elevated more than 3-fold the normal upper limit) (*18*). A surgical site infection, urinary tract infection, or pneumonia were all considered infectious complications. The Clavien-Dindo classification was used to classify the severity of each postoperative complication.

2.4. Data collection and follow-up

The baseline characteristics of the patients included their age, sex, comorbidities, carcinoembryonic antigen (CEA), the maximum tumor size, and TNM stage. Chemotherapy-related variables included NAC cycles and targeted therapy. Surgery-related variables included the procedure (open or endoscopic), range of hepatectomy (minor or major), intraoperative blood loss, and operating time. The follow-up cut-off date was set at January 31, 2022. Follow-up examinations should consist of a serology based on tumor markers, as well as contrast-enhanced CT or MRI scans. These evaluations should be conducted every 3 months in the first 2 years, and then every 6 months for up to 5 years. If recurrence is detected, the subsequent treatment can be determined based on the effectiveness of preoperative NAC, or other treatments such as radiofrequency ablation or TACE were available.

2.5. Statistical analysis

The statistical software SPSS (IBM SPSS, version 25.0) was used for statistical analysis. Continuous variables were expressed as the median and interquartile range (IQR), while categorical variables were expressed as numbers with percentages. The Mann-Whitney *U* test was used to compare continuous variables between groups, while Pearson's chi-squared test was used to compare categorical variables. A P value of < 0.05 was considered to be significant. An analysis of differences in OS and RFS was performed using the Kaplan-Meier method. X-tile (Yale University School of Medicine, New Haven, Connecticut, USA) (*19*) was used to analyze the survival data to determine the appropriate cut-off value for grouping. Logistic regression was used for univariate analysis, and multivariate analysis was performed with factors with a P value < 0.1 from univariate analysis. Multivariate analysis using logistic regression included a number of variables, and variables with a $P < 0.05$ were considered independent predictors of postoperative complications.

3. Results

3.1. Clinical characteristics

A total of 141 patients with CRLM consisted of 104 males and 37 females, and the median age was 58.0

years (IQR: 50-66). Sixty-five patients (46.1%) had primary tumors located in the colon. Forty-five tumors were in the left colon and 20 were in the right colon. Synchronous liver metastases were diagnosed in 110 patients (78.0%). Multiple liver metastases were noted in 97 patients (68.8%). Oxaliplatin-based regimens were used in 103 patients (73.0%). Moreover, 45 patients (31.9%) received targeted drugs (22 bevacizumab and 23 cetuximab) as well. All details are listed in Table 1.

3.2. The best cut-off value for the timing of surgery

X-tile analysis was used to determine the best cut-off value for CFI based on patients' RFS (Figure 1). The optimal point of CFI was4 weeks, which was determined to be the best cut-off point for the interval for predicting recurrence. Thus, all patients were divided into two groups: a short interval group (SIG, ≤ 4 weeks, n = 98) and a long interval group (LIG, > 4 weeks, n = 43). The clinicopathologic characteristics are summarized in Table S1 (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=143*). There were no significant differences between the two groups in albumin levels, body mass index (BMI), comorbidities, preoperative CEA levels, the diameter of metastases, whether liver resection was major or minor, or other factors.

3.3. Clinical characteristics of subgroups

Table 1. Baseline characteristics of patients

Items	n = 141 (%)
Patient-related variables	
Age > 60 years	63 (44.7)
Male	104 (73.8)
BMI > 24	43 (30.5)
Comorbidity	46 (32.6)
ALB > 40 g/L	109 (77.3)
Child-Pugh A classification	140 (99.3)
Tumor-related variables	
CEA > 3 0ng/mL	37 (26.2)
Synchronous liver metastasis	110 (78.0)
Colon	65 (46.1)
Multiple liver metastasis	97 (68.8)
Diameter of metastases > 5 cm	27 (19.1)
T3-4	134 (95.0)
Node-positive primary tumor	104 (73.8)
Poor differentiation	36 (25.5)
Chemotherapy-related variables	
OX-based regimens	103 (73.0)
NAC toxicity	22 (15.6)
NAC cycle > 6	33 (23.4)
Targeted therapy	45 (31.9)
Procedure-related variables	
Simultaneous resection	7 (5.0)
Major liver resection	58 (41.1)
Open surgery	41 (29.1)

BMI: body mass index; ALB: albumin; CEA: carcinoembryonic antigen; T3-4: The TNM staging of colorectal cancer primary tumor is stage 3 or 4; OX: oxaliplatin; NAC: neoadjuvant chemotherapy.

Subgroup analysis was performed to determine the incidence of postoperative complications in different CFI. To further analyze the incidence of complications within 4 weeks, the SIG group was divided into three subgroups: a CFI of 1-2 weeks, a CFI of 2-3 weeks, and a CFI of 3-4 weeks. Doing so allowed investigation of the incidence of postoperative complications that occurred within a 4-week period in each of these subgroups. The clinicopathologic characteristics of subclassification are shown in Table 2. There were no marked differences in clinicopathologic characteristics between subgroups, except for the albumin level, chemotherapy regimen, and targeted therapy. In addition, there were no significant differences in the albumin level and chemotherapy regimen between the SIG and LIG.

3.4. Short-term outcomes in subgroups

Intraoperative findings in the 4 groups are shown in Table 3. No intraoperative mortality occurred. Intraoperative bleeding, the operating time, and the duration of postoperative hospitalization did not differ significantly among the 4 groups.

A total of 29 patients developed postoperative complications, which occurred in 23 patients (23.5%) in the SIG and 6 patients (14.0%) in the LIG (P =

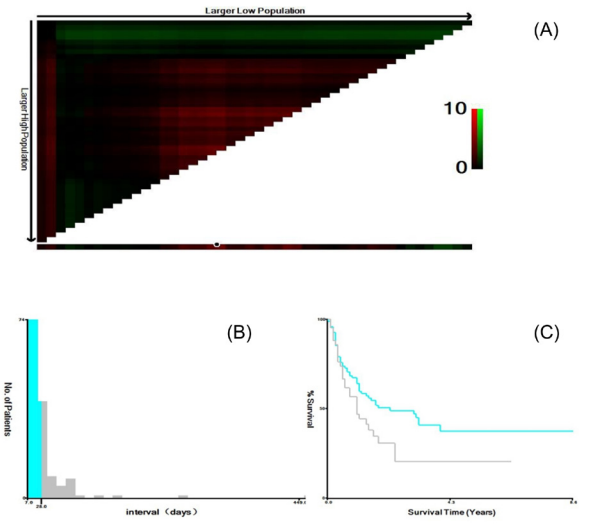

Figure 1. X-tile plots of the interval between finishing neoadjuvant chemotherapy and liver resection. X-tile plots show log-rank values with cut points, with the data divided into low and high groups. (A), The X-axis represents all potential cut-off values from low to high that define a low subset, whereas the Y-axis represents cut-off values from high to low that define a high subset. Red coloration of cut-off values indicates an inverse correlation with time to recurrence, and green coloration represents direct associations. The optimal cut-off value occurs at the brightest pixel according to a chi-square test. **(B)**, A histogram of the entire cohort divided into low and high subgroups depending on the optimal cut-off value (4 weeks). **(C)**, A Kaplan-Meier plot of RFS produced by the optimal cut-off value of CFI. Blue represents the SIG, and gray represents the LIG.

Table 2. Baseline characteristics in subgroups

Items	1-2 weeks *n* = 20 (%)	2-3 weeks *n* = 41 (%)	3-4 weeks *n* = 36 (%)	> 4weeks *n* = 43 (%)	*P*
Patient-related variables					
Age > 60 years	5 (25)	22 (53.7)	16 (44.4)	20 (46.5)	0.211
Male	12 (60)	33 (80.5)	23 (63.9)	36 (83.7)	0.072
BMI > 24	5 (25)	10 (24.4)	16 (44.4)	12 (27.9)	0.219
Comorbidity	7 (35)	13 (31.7)	10 (27.8)	15 (34.9)	0.910
ALB > 40g/L	15 (75)	26 (63.4)	33 (91.7)	35 (81.4)	0.025
Child-Pugh A classification	20 (100)	40 (97.6)	36 (100)	43 (100)	0.488
Tumor-related variables					
CEA > 30 ng/mL	6 (30)	9 (22)	12 (33.3)	10 (23.3)	0.646
Synchronous liver metastasis	18 (90.0)	30 (73.2)	29 (80.6)	32 (74.4)	0.444
Colon	10 (50)	21 (51.2)	14 (38.9)	19 (44.2)	0.714
Multiple liver metastasis	13 (65.0)	30 (73.2)	24 (66.7)	30 (69.8)	0.900
Diameter of metastases > 5 cm	5 (25)	7 (17.1)	8 (22.2)	7 (16.3)	0.802
T3-4	20 (100)	36 (87.8)	35 (97.2)	42 (97.7)	0.088
Node-positive primary tumor	17 (85.0)	29 (70.7)	26 (72.2)	31 (72.1)	0.660
Poor differentiation	4 (20)	10 (24.4)	8 (22.2)	14 (32.6)	0.645
Chemotherapy-related variables					
OX-based regimens	19 (95.0)	34 (82.9)	22 (61.1)	28 (65.1)	0.012
NAC toxicity	2 (10)	10 (24.4)	3 (8.3)	7 (16.3)	0.229
NAC cycle > 6	5 (25.0)	10 (24.4)	8 (22.2)	10 (23.3)	0.994
Targeted therapy	5 (25.0)	8 (19.5)	9 (25.0)	23 (53.5)	0.004
Procedure-related variables					
Simultaneous resection	1 (5.0)	1 (2.4)	4 (11.1)	1 (2.3)	0.257
Major liver resection	7 (35.0)	18 (43.9)	16 (44.4)	17 (39.5)	0.887
Open surgery	16 (80.0)	32 (78.0)	23 (63.9)	29 (67.4)	0.401

BMI: body mass index; ALB: albumin; CEA: carcinoembryonic antigen; T3-4: The TNM staging of colorectal cancer primary tumor is stage 3 or 4; OX: oxaliplatin; NAC: neoadjuvant chemotherapy.

Table 3. Short-term outcomes in subgroups

Items	1-2 weeks (*n* = 19)	2-3 weeks (*n* = 40)	3-4 weeks (*n* = 33)	> 4 weeks (*n* = 41)	*P*
Intraoperative bleeding (mL); median (IQR)	200 (100-400)	350 (100-575)	200 (100-400)	300 (150-400)	0.453
Operating time (min); median (IQR)	152 (104-186)	148 (123.25-203)	142 (113-231.5)	166 (130-202)	0.535
Duration of postoperative hospitalization (days); median (IQR)	8 (6.25-11.75)	7 (6-10)	7 (5-10.5)	8 (6-10)	0.626

IQR: inter-quartile range

Table 4. Postoperative complications in subgroups

Complications	1-2 weeks *n* = 20 (%)	2-3 weeks *n* = 41 (%)	3-4 weeks *n* = 36 (%)	> 4 weeks *n* = 42 (%)	*P*
Overall	7 (35.0)	8 (19.5)	8 (22.2)	6 (14.3)	0.288
Abdominal infection	2 (10.0)	4 (9.8)	2 (5.6)	1 (2.4)	
Surgical site infection	1 (5.0)	0 (0.0)	1 (2.8)	1 (2.4)	
Urinary tract infection	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	
Postoperative bleeding	1 (5.0)	2 (4.9)	0 (0.0)	3 (7.1)	
Bile leak	0 (0.0)	1 (2.4)	1 (2.8)	0 (0.0)	
Hepatic insufficiency	0 (0.0)	1 (2.4)	1 (2.8)	0 (0.0)	
Pleural effusion	3 (15.0)	0 (0.0)	3 (8.3)	2 (4.8)	
Ileus	0 (0.0)	0 (0.0)	0 (0.)	1 (2.4)	

0.198). All postoperative complications were mild. No mortality was reported within 30 days postoperatively. Although the incidence of postoperative complications in the CFI of 1-2 weeks group was higher than that in the CFI of > 4 weeks group (35% *vs*. 14.3%, $P = 0.055$), the difference was not significant. The complications that occurred are shown in Table 4.

The association between postoperative complications and baseline characteristics is shown in Table 5. In univariate analyses, a CFI of 1-2 weeks ($P = 0.062$) and ALB ≤ 40 g/L ($P = 0.025$) were associated with complications. In multivariate analyses, a CFI of 1-2 weeks (OR = 0.263, 95% CI:2.70-0.985, $P = 0.048$) and ALB > 40 g/L (OR = 0.341, 95% CI:0.124-0.945,

Table 5. Prognostic factors for postoperative complications

Items	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
interval > 4 weeks	*ref*		*ref*	
interval of 3-4 weeks	0.568 (0.177-1.823)	0.341	0.516 (0.148-1.799)	0.299
interval of 2-3 weeks	0.669 (0.210-2.129)	0.496	1.154 (0.319-4.167)	0.827
interval of 1-2 weeks	0.301 (0.085-1.062)	0.062	0.263 (0.70-0.985)	0.048
Age > 60 years	1.406 (0.620-3.191)	0.415		
Male	1.111 (0.430-2.874)	0.827		
BMI > 24	0.663 (0.259-1.695)	0.391		
Comorbidity	0.611 (0.240-1.559)	0.303		
ALB > 40 g/L	0.360 (0.147-0.878)	0.025	0.341 (0.124-0.945)	0.038
CEA > 30 ng/mL	1.077 (0.430-2.697)	0.874		
Synchronous liver metastasis	2.009 (0.642-6.288)	0.231		
Colon	1.615 (0.710-3.677)	0.253		
Multiple metastasis	0.663 (0.259-1.695)	0.391		
Simultaneous resection	3.087 (0.650-14.645)	0.156		
Diameter of metastases > 5cm	1.845 (0.712-4.781)	0.208		
Major liver resection	1.192 (0.523-2.717)	0.677		
T3-4	1.600 (0.185-13.841)	0.669		
Node-positive primary tumor	0.501 (0.210-1.194)	0.119		
Targeted therapy	1.384 (0.590-3.244)	0.455		
Child-Pugh A classification	/	/		
NAC toxicity	2.639 (0.982-7.093)	0.054	2.640 (0.849-8.215)	0.094
NAC cycle > 6	1.040 (0.399-2.709)	0.936		
Poor differentiation	1.129 (0.450-2.834)	0.796		
Open surgery	0.591 (0.221-1.582)	0.295		

BMI: body mass index; ALB: albumin; CEA: carcinoembryonic antigen; T3-4: The TNM staging of colorectal cancer primary tumor is stage 3 or 4; OX: oxaliplatin; NAC: neoadjuvant chemotherapy.

P = 0.038) were definitely independent indicators for postoperative complications.

3.5. Survival analysis

Seventy-nine patients (56%) experienced tumor recurrence, and 31.2% of patients had died before the cut-off time. Median OS was 35 months (IQR:26-55), and median RFS was 13 months (IQR:5-26). Patients in the SIG were more likely to have significantly better RFS (3-year RFS 47.4% *vs*. 20.5%, *P* = 0.043) (Figure 2A). There were no significant differences in RFS among the 4 subgroups (*P* = 0.103). However, the median RFS of patients with a CFI of 3-4 weeks was 17 months (IQR: 22.35-38.75) *vs*. 12 months (IQR:4.5-18.5) for patients with a CFI of > 4 weeks (*P* = 0.01) (Figure 2B). There were no significant differences in OS among the 4 subgroups (Figure 2C).

4. Discussion

To the extent known, the proper timing for patients with CRLM to undergo hepatectomy after their last chemotherapy had never been defined. Published guidelines and consensus opinions were consulted for this study, but none recommended a proper interval between the last NAC and surgery. Two aspects of the interval need to be taken into account.

Initially, anti-cancer drugs can result in varying degrees of hepatocellular injuries, such as oxaliplatin-induced hepatic sinusoidal dilatation and irinotecan-induced fatty liver (*20,21*). The primary concern with reducing the preoperative CFI was that liver injury caused by chemotherapy drugs may affect the surgical process and postoperative recovery (including increased intraoperative bleeding and a longer operating time) (*22*). However, Takeshi *et al*. (23) reported that liver function will return to normal after more than 2-4 weeks following the cessation of chemotherapy. Welsh *et al*. (*17*) found that patients who had liver resection within 4 weeks of NAC had the highest incidence of postoperative complications. This is consistent with the finding of the current study that an increase in postoperative complications in patients with a CFI of up to 4 weeks mainly occurred in patients with a CFI of up to 2 weeks.

In addition, NAC was considered to be the standard treatment for CRLM before surgery based on published studies (*24-27*). However, a prolonged CFI may increase the chances of recurrence and worsen prognosis (*28*). Adam *et al*. (*29*) found that disease progressed in about 25% of patients during the interval between NAC and surgery. Another study found that the cohort of patients who underwent resection more than 5 weeks after NAC, compared to the group that underwent less than 5 weeks after, had a worse pathological reaction and worse RFS (*30*). Thomas *et al*. (*13*) concluded that surgery within 2 months of NAC improved long-term outcomes.

In the current study, 4 weeks was the appropriate cut-off point for the assignment of patients to the SIG or LIG by X-tile analysis. In terms of short-term outcomes, there were no significant differences

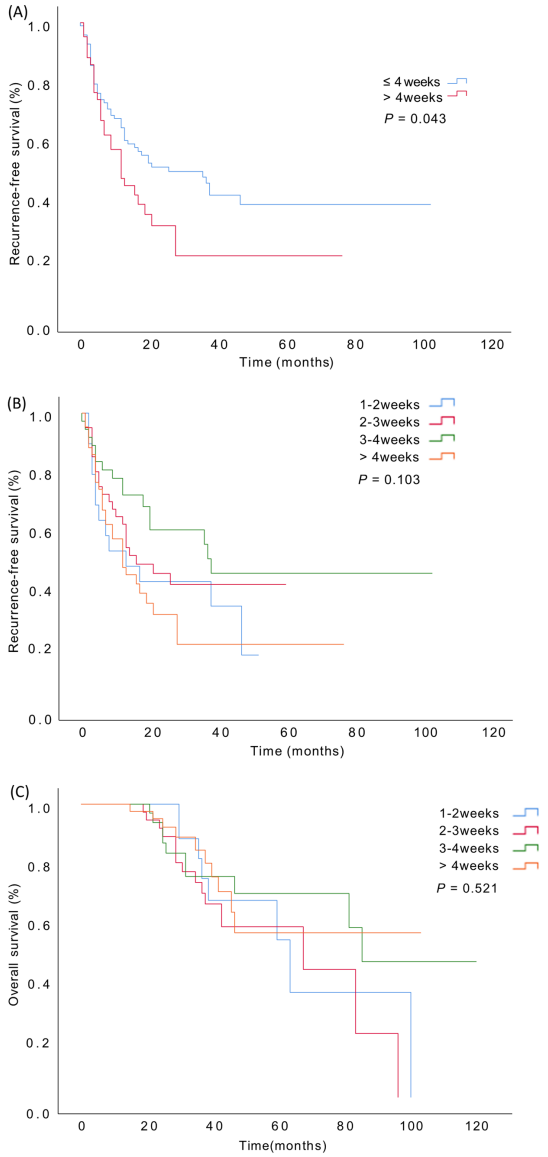

Figure 2. (A), Kaplan-Meier survival curve for RFS of the SIG and LIG. (B), Kaplan-Meier survival curve for RFS of subgroups. (3-4weeks *vs.* > 4weeks $p = 0.01$). (C), Kaplan-Meier survival curve for OS of subgroups.

between subgroups, including intraoperative bleeding, operating time, and the duration of postoperative hospitalization. Outcomes revealed that short intervals after NAC did not worsen perioperative data. However, the postoperative complication rate in the 1-2 weeks subgroup was marginally higher than that in the > 4 weeks subgroup (35% *vs*. 14.3% $P = 0.055$) according to subgroup analyses. In addition, 1-2 weeks was an independent indicator for postoperative complications according to multivariate analyses.

The current study found that patients in the SIG had a better 3-year RFS (47.4% *vs*. 20.5%, $P = 0.043$). However, the 3-year OS was not correlated with the length of the interval (76.1% in the SIG *vs*. 79.9% in the LIG, $P = 0.635$). Differences between RFS and OS might be explained by several factors. To start with, recurrence of colorectal cancer after hepatic resection was caused by the unique biological characteristics of the disease, since liver metastasis will be detected in about half of patients as the disease progresses. RFS does not intuitively reflect the OS (*31,32*). Oba *et al*. argued that the time to recurrence of an unresectable tumor is strongly associated with the OS (33). The OS is a composite endpoint that is heavily affected by treatment, whether conservative or surgical (*24*). Although tumor progression leading to patient death remains the primary cause of mortality, the prolonging of OS has resulted in an increase in non-tumor-related deaths. This is also a significant factor affecting the differences between the RFS and OS. More chemotherapy drugs and targeted drugs are often used during the first recurrence in patients electing to undergo surgery, and this could have affected the OS. The development and use of tumor immune targeted therapy has reduced the role of surgery in the patient's prognosis and significantly improved OS (*34,35*).

This study found that a CFI < 4 weeks is associated with better RFS, and 1-2 weeks was an independent factor influencing the development of complications. Having balanced postoperative complications and oncological outcomes, the best interval between NAC and surgery was 2-4 weeks. Other studies have also indicated that the appropriate timing of surgery after NAC improved patient prognosis. Although factors such as chemotherapy regimens and targeted drug use will affect the interval, the impact of other factors on the CFI should be minimized.

As a single-center retrospective study, the current study has several limitations. First, bias with respect to the determination of resectability by different doctors could not be completely ruled out. All of the current patients had resectable CRLM, the toxicity of NAC, whether targeted therapy was used or not, and the patient's performance status may have influenced the timing of surgery. Second, there were differences in the choice of chemotherapy regimens in the 2 groups, and the decision was generally reached through conversations between patients and their doctors. Targeted drugs such as bevacizumab need to be stopped for more than 6 weeks, which is also a factor affecting the operating time. Third, this study had a small sample size. Larger samples and multicenter randomized controlled trials are needed to confirm the current results.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received October 11, 2022; Revised March 7, 2023; Re-revised April 8, 2023; Accepted April 18, 2023.

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Released online in J-STAGE as advance publication April 22, 2023.