What is the optimal number of neoadjuvant chemotherapy cycles for resectable colorectal liver oligometastases?

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Background: The optimal number of neoadjuvant chemotherapy (NAC) cycles for resectable colorectal liver oligometastases (CLOM) remains unclear. The aim of this study was to investigate the optimal number of NAC cycles.

Methods: One hundred twenty-nine consecutive patients were included in this study. X-tile analysis was implemented to investigate the optimal cut-off point for NAC cycles. Propensity score matching was performed to reduce selection bias. Kaplan-Meier curves and Cox risk regression models were used to analyse progression-free survival (PFS) and overall survival (OS).

Results: The optimal cut-off point for NAC cycles was 5. There were no significant differences in R0 resection, pathological response or postoperative complications between the groups with a low number of NAC cycles group (≤5 cycles, n=80) and high number of NAC cycles (>5 cycles, n=49). Patients with a high number of NAC cycles were more likely to have NAC toxicity than those with a low number of cycles (87.8% *vs.* 65.0%, P=0.004). Multivariate analysis revealed that >5 NAC cycles was an independent predictor of reduced PFS (HR =1.808, 95% CI: 1.205–2.712, P=0.004) and reduced OS (HR =1.723, 95% CI: 1.041–2.851, P=0.034). In the oxaliplatin-based regimen group, patients with a low number of NAC cycles had a better PFS (P<0.001, mPFS: 14.7 *vs.* 5.4 months) and better OS (P=0.018, mOS: 57.7 months *vs.* 41.0 months) than those with a high number of cycles. After 1:1 propensity matching (34 cases *vs.* 34 cases), multivariate analysis revealed that >5 NAC cycles was an independent predictor of reduced PFS (HR =2.265, 95% CI: 1.281–4.007, P=0.005) and reduced OS (HR =2.813, 95% CI: 1.359–5.822, P=0.005). In the oxaliplatin-based regimen group, patients with a low number of NAC cycles had better PFS (P<0.001, mPFS: 17.5 *vs.* 5.6 months) and better OS (P=0.008, mOS: 59.0 *vs.* 31.8 months) than those with a high number of cycles.

Conclusions: Fewer than 5 NAC cycles was optimal for biologically resectable CLOM patients. Giving more than 5 NAC cycles was unnecessary because a higher number of NAC cycles has more unfavourable survival and higher NAC toxicities, while leading to similar R0 resection rates and pathological responses.

Keywords: Colorectal liver oligometastases (CLOM); neoadjuvant chemotherapy (NAC); cycles; outcomes

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Introduction

Colorectal cancer is the fourth most common malignant tumour worldwide and the second leading cause of cancer-related death (1). The liver is the most common metastatic organ for colorectal cancer. Liver metastasis is found in 15–25% of colorectal cancer patients upon diagnosis, while another 15–25% of patients have liver metastasis after primary colorectal cancer resection (2,3). Liver resection is the most effectively curative treatment for colorectal cancer liver metastasis (CRLM) patients, with a 5-year survival rate of 43% (4).

The 2016 ESMO guidelines divided metastatic colorectal cancer into two categories: oligometastatic disease and widespread systemic disease (5). Oligometastasis refers to an intermediate state in the process of tumour metastasis. It is a relatively early stage of biological invasion between localized primary tumours and widespread metastatic tumours. Oligometastatic disease confined to the liver is potentially curable. Aggressive local treatments, especially liver resection, may prolong the survival of patients with colorectal liver oligometastases (CLOM), leading to a 5-year overall survival (OS) rate of 45.9% (6,7). Neoadjuvant chemotherapy (NAC) can treat micrometastases, reduce the burden of tumours, and improve the rate of R0 resection (8). For biologically resectable CLOM patients, NAC is increasingly used as a potentially effective treatment strategy. However, it is still unclear how many cycles of NAC are needed to obtain the maximum benefits for biologically resectable CLOM. Some studies have shown that more than eight or more than nine cycles of NAC for CRLM patients did not add any benefit and led to the increased postoperative liver insufficiency and toxicities (9,10). The National Comprehensive Cancer Network (NCCN) guidelines (11) recommend the option of NAC for resectable CRLM for a period of 2–3 months but do not specify how many cycles of NAC would benefit patients the most.

The optimal number of NAC cycles is vital for CLOM patients. Too many NAC cycles may lead to more NAC toxicities, increase the incidence of postoperative complications (10,12) and potentially increase the risk of progression. An insufficient number of NAC cycles cannot achieve the maximum benefits from neoadjuvant therapy. To address this question, this study was conducted to investigate the optimal number of NAC cycles for patients with biologically resectable CLOM. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4289).

Methods

All participants gave informed consent before taking part in this study. This study was conducted with approval from the Institute Research Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences (ID: NCC2019C-016). The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

Patient population

We retrospectively examined data from 407 CRLM patients who underwent primary liver resection at the Cancer Hospital, Chinese Academy of Medical Sciences, from December 2006 to May 2018. The final enrolled patients met the following inclusion criteria: (I) pathologically confirmed CRLM; (II) treatment with NAC; (III) colorectal liver oligometastases (≤5 liver metastases and no preoperative extrahepatic metastases) (5,7); and (IV) biological resectability (remaining liver volume more than 30–40% after liver resection). We excluded 278 patients based on the inclusion criteria: no prior NAC (n=194); non-biologically resectable colorectal liver oligometastases (n=60); treatment with neoadjuvant radiotherapy (n=14) and lost to follow-up or incomplete clinical data (n=10). The final cohort consisted of 129 patients (*Figure 1*). Comorbidity was defined as chronic diseases (e.g., diabetes mellitus or pulmonary, cardiovascular, and other diseases).

Treatment

Patients received NAC with oxaliplatin- or irinotecan-based regimens, such as FOLFOX (5-fluorouracil/leucovorin/oxaliplatin), XELOX (capecitabine/oxaliplatin) or FOLFIRI (5-fluorouracil/ leucovorin/irinotecan). The targeted therapy regimens combined with NAC included bevacizumab or cetuximab. The NAC regimens, number of NAC cycles and timing of surgery were determined by a multidisciplinary team (MDT) including surgeons, oncologists, pathologists and imaging physicians, as previously described (13,14). NAC regiments were determined according to the characteristics of these regimens and the specific conditions of patients. When determining the number of NAC cycles for CRLM, the

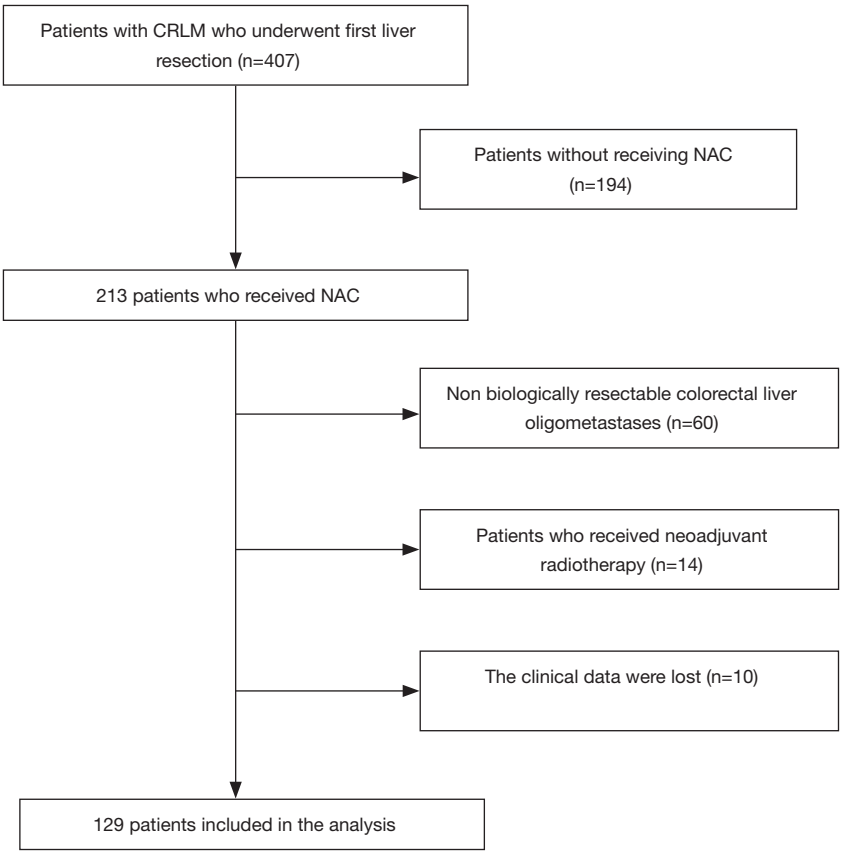

Figure 1 Flow diagram for the selection of CLOM in this study. CLOM, colorectal liver oligometastases; CRLM, colorectal cancer liver metastasis; NAC, neoadjuvant chemotherapy.

MDT may consider several factors including surgical difficulties, the efficacy of NAC, the NAC toxicities and the physical conditions of patients. The decision on the number of NAC cycles is a comprehensive consideration and varies for each patient. The MDT team will make the appropriate choice based on the characteristics of each patient. The postoperative chemotherapy regimens and the number of cycles depended on the NAC response, NAC cycles and tumour pathology. Tumour regression was graded as described by tumour regression grades (TRGs) (15). Tumour regression grades 1–3 were defined as favourable tumour responses, and grades 4–5 were defined as poor tumour responses. NAC toxicity was assessed according to the NCI-CTCAE (version 4.0).

R0 resection was defined as resected tumour lesions with a surgical margin of more than 1 mm. Major liver resections were defined as resections of more than two liver segments. CRLM resection included simultaneous CRLM resection and heterochronous CRLM resection. Simultaneous resection was described as both primary and metastatic tumours resected at the same time. The postoperative complications were categorized by the Dindo-Clavien classification (16), with minor complications defined as grade I or II and major complications defined as grade III, IV, or V.

Follow-up and outcome

All patients were followed up 1 month after surgery, every 3 months thereafter. At each follow-up, CT or MRI scan, serum carcinoembryonic antigen (CEA) measurement and liver function test were routinely conducted. The tumor progression was evaluated by imaging and serum CEA measurement. After tumor progression, patients received surgery, radiofrequency ablation, transcatheter arterial chemoembolization, chemotherapy or targeted therapies, as appropriate. OS was defined as the time from surgery to death (all causes) or date of last follow-up. PFS was defined

as the time from surgery to the first recorded evidence of progression, in cases without progression, to the last follow-up data or death.

Statistical analysis

Categorical variables are presented as frequencies with percentages, and continuous variables are presented as medians with interquartile ranges (IQRs). The perioperative clinicopathologic characteristics were compared using the χ^2 and Mann-Whitney U tests, as appropriate. X-tile analysis (17) was implemented to investigate the optimal cut-off point for the number of NAC cycles. Propensity score matching was performed to reduce selection bias and quantify the possible associations between clinicopathologic characteristics and survival. To minimize the impact of other confounding factors on prognosis, we used a propensity score analysis to match these two types of patients (patients with NAC cycles ≤5 and patients with NAC cycles >5) in a 1:1 ratio using the nearest neighbor matching. The confounders used for matching included major liver resection, multiple metastases, NAC toxicity and targeted therapy. This study used the Kaplan-Meier method to estimate the progression-free survival (PFS) and overall survival (OS) of all patients and statistically compared the data with log-rank tests. A forward LR Cox regression model was created to identify prognostic factors influencing OS and PFS, with results presented as hazard ratios (HRs) with 95% confidence intervals (95% CI). Variables with P<0.10 in univariable analysis were included in the multivariable analysis. All analyses were performed using SPSS, version 22 software (Armonk, NY, USA). P<0.05 was considered significant.

Results

Patients

The detailed baseline characteristics of the included patients are shown in *Table 1*. A total of 129 patients were included, including 75 males and 54 females, with a median age of 56 years (IQR, 49–63, range, 28–79). Forty-seven patients (36.4%) were aged older than 60 years. A BMI >24 kg/m^2 was observed in 60 patients. The primary tumour site was the rectum in fifty-seven patients (44.2%). Positive lymph nodes were found in more than half of the patients (60.5%). The stage pN1 tumours were observed in 53 patients, and stage pN2 tumours were observed in 25 patients. Stage pT3-pT4 tumours were observed in 83.7% of the patients. A single liver metastasis was present in 43 patients (33.3%) *vs.* multiple metastases in 86 patients (66.7%), with a median of 2 metastases (IQR, 1.0–3.0, range, 1–5). The maximum diameter of the largest liver lesion was >3 cm in 61 patients, with a median diameter of 2.7 cm (IQR, 1.8–4.0); 87.6% of the patients had synchronous liver metastases. A total of 44.2% of the patients had a bilobar distribution of liver lesions.

Neoadjuvant chemotherapy and operative details

The median number of NAC cycles was 4 (IQR, 3–6). An oxaliplatin-based regimen was administered for 95 patients (73.6%), and targeted therapy was added in 41 cases (31.8%). NAC toxicities were observed in 95 patients (73.6%), including 53 patients with haematologic toxicities and 59 patients with gastrointestinal toxicity. A total of 52 patients had neutropenia, and 9 patients had liver toxicity. There was no mortality due to NAC toxicity. Fifty-two patients (40.3%) had a favourable histological response (TRG 1-3). Seventy-four patients (57.4%) were treated with postoperative chemotherapy. Major resection was performed in 61 patients (47.3%), while minor liver resection was performed in 68 patients (52.7%). Thirty-one patients underwent heterochronous resection. R0 resection was achieved in 93 patients (72.1%).

Clinicopathologic characteristics of the groups with a high number of NAC cycles group and a low number of NAC cycles

X-tile software was used to determine that 5 was the optimal cut-off value for the number of NAC cycles (*Figure 2*). Based on the number of NAC cycles, 129 patients were classified into the group with a low number of NAC cycles (≤5 cycles, n=80) and the group with a high number of NAC cycles (>5 cycles, n=49). In the group with a low number of NAC cycles, the median NAC cycles was 3.5 (IQR, 2.0–4.0). In the group with a high number of NAC cycles, the median NAC cycles was 7 (IQR, 6.0–8.5). The associations between NAC cycles and various clinicopathological features are shown in *Table 1*.

There were no significant differences in the R0 resection rate, pathological response, pT stage, presence of node-positive primary tumour, preoperative CEA, metastasis diameter or bilobar distribution between the groups with a low number of NAC cycles group and a high number of

Table 1 Patient and tumour characteristics

Item	Before propensity matching				After propensity matching			
	NAC cycles ≤5 (n=80), n (%)	NAC cycles >5 (n=49), n (%)	P	All patients (n=129), n (%)	NAC cycles ≤5 (n=34), n (%)	NAC cycles >5 (n=34), n (%)	P	All patients (n=68), n (%)
Age >60 years	32 (40.0)	15 (30.6)	0.282	47 (36.4)	12 (35.3)	11 (32.4)	0.798	23 (33.8)
Male	46 (57.5)	29 (59.2)	0.851	75 (58.1)	19 (55.9)	22 (64.7)	0.457	41 (60.3)
BMI >24 kg/m^2	35 (43.8)	25 (51.0)	0.422	60 (46.5)	15 (44.1)	15 (44.1)	1.000	30 (44.1)
Comorbidity	34 (42.5)	20 (40.8)	0.851	54 (41.9)	13 (38.2)	13 (38.2)	1.000	26 (38.2)
ASA score 3-4	9 (11.3)	7 (14.32)	0.612	16 (12.4)	3 (8.8)	5 (14.7)	0.452	8 (11.8)
Preoperative CEA >10 ng/mL	33 (41.3)	19 (38.8)	0.781	52 (40.3)	16 (47.1)	14 (41.2)	0.625	30 (44.1)
Synchronous metastasis	70 (87.5)	43 (87.8)	0.966	113 (87.6)	29 (85.3)	30 (88.2)	0.720	59 (86.8)
Left hemicolon	72 (90.0)	39 (79.6)	0.98	111 (86.0)	29 (85.3)	28 (82.4)	0.742	57 (83.8)
R0 resection	59 (73.8)	34 (69.4)	0.592	93 (72.1)	28 (82.4)	24 (70.6)	0.253	52 (76.5)
Major liver resection	32 (40.0)	29 (59.2)	0.034	61 (47.3)	18 (52.9)	23 (67.6)	0.215	41 (60.3)
Heterochronous resection	16 (20.0)	15 (30.6)	0.171	31 (24.0)	5 (14.7)	11 (32.4)	0.086	16 (23.5)
Bilobar distribution	31 (38.8)	26 (53.1)	0.112	57 (44.2)	16 (47.1)	21 (61.8)	0.223	37 (54.4)
Diameter of metastases >3 cm	34 (42.5)	27 (55.1)	0.164	61 (47.3)	17 (50.0)	21 (61.8)	0.329	38 (55.9)
Multiple metastases	47 (58.8)	39 (79.6)	0.015	86 (66.7)	27 (79.4)	30 (88.2)	0.323	57 (83.8)
Poor differentiation	18 (22.5)	11 (22.4)	0.995	29 (22.5)	9 (26.5)	9 (26.5)	1.000	18 (26.5)
T3-T4 stage	68 (85.0)	40 (81.6)	0.615	108 (83.7)	26 (76.5)	27 (79.4)	0.770	53 (77.9)
Node-positive primary tumor	48 (60.0)	30 (61.2)	0.890	78 (60.5)	20 (58.8)	22 (64.7)	0.618	42 (61.8)
NAC toxicity	52 (65.0)	43 (87.8)	0.004	95 (73.6)	29 (85.3)	29 (85.3)	1.000	58 (85.3)
KRAS mutation[a]	13 (16.3)	10 (20.4)	0.550	23 (17.8)	7 (20.6)	7 (20.6)	1.000	14 (20.6)
Preoperative chemotherapy								
Oxaliplatin-based regiment	62 (77.5)	33 (67.3)	0.336	95 (73.6)	29 (85.3)	23 (67.6)	0.117	52 (76.5)
Irinotecan-based regiment	9 (11.3)	6 (12.2)		15 (11.6)	3 (8.8)	3 (8.8)		6 (8.8)
Oxaliplatin + irinotecan	9 (11.3)	10 (20.5)		19 (14.8)	2 (5.9)	8 (23.6)		10 (14.7)
Targeted therapy	14 (17.5)	27 (55.1)	<0.001	41 (31.8)	11 (32.4)	12 (35.3)	0.798	23 (33.8)
Pathological response	30 (37.5)	22 (44.9)	0.406	52 (40.3)	16 (47.1)	12 (35.3)	0.324	28 (41.2)
Post-operative complications	40 (50.0)	24 (49.0)	0.910	64 (49.6)	19 (55.9)	17 (50.0)	0.627	36 (52.9)
Postoperative chemotherapy	49 (61.3)	25 (51.0)	0.254	74 (57.4)	22 (64.7)	19 (55.9)	0.457	41 (60.3)

[a], KRAS status was available in 76 patients before propensity matching and in 44 patients after propensity matching. NAC, neoadjuvant chemotherapy; BMI, body mass index; ASA, American society of anesthesiologists physical status classification; CEA, carcinoembryonic antigen.

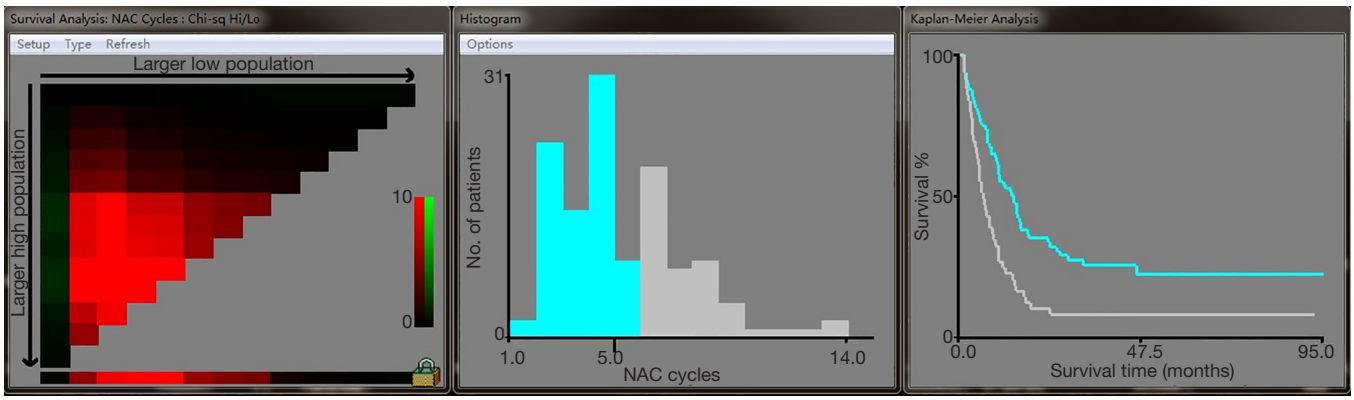

Figure 2 X-tile plots of the NAC cycles and the PFS of patients with CLOM who underwent curative resection. The optimal cut-off value of the NAC cycles was 5. Histogram of the entire cohort divided into a low number of NAC cycles and a high number of NAC cycles subgroups according to the optimal cut-off value of 5. Blue bars represent the low NAC cycles group, and grey bars represent the high NAC cycles group. Kaplan-Meier plot of PFS in groups stratified using the optimal cut-off value of NAC cycles. Blue curves represent the low NAC cycles group, and grey curves represent the high NAC cycles group. NAC, neoadjuvant chemotherapy; PFS, progression-free survival.

NAC cycles. In contrast, compared to patients with a low number of NAC cycles, patients with a high number of NAC cycles were more likely to have NAC toxicity (87.8% *vs.* 65.0%, P=0.004), multiple liver metastases (79.6% *vs.* 58.8%, P=0.015) and major liver resection (59.2% *vs.* 40.0%, P=0.034).

To eliminate bias between the two groups, 1:1 propensity matching was conducted. The analysis of heterogeneity after propensity matching between 34 patients with a high number of NAC cycles and 34 patients with a low number of NAC cycles revealed an almost equal distribution of the following characteristics: age, ASA score, complications, NAC toxicity, number of liver metastases and surgery strategy (*Table 1*).

Association between NAC cycles and postoperative complications

No perioperative mortality occurred, and 64 patients (49.6%) experienced complications (27 major complications; 37 minor complications). No liver failure was observed in this study. In the group with a low number of NAC cycles, 40 patients developed complications (17 major complications and 23 minor complications). In the group with a high number of NAC cycles, 24 patients developed complications (10 major complications and 14 minor complications). We further investigated the complication rates to address the question of whether patients with a high number of NAC cycles suffered from a higher incidence of postoperative complications. No difference in postoperative complications (P=0.910), minor complications (P =0.983) or major complications (P=0.909) was observed between the two groups.

Association between the number of NAC cycles and survival

Before 1:1 propensity matching

The median follow-up time was 46 months. One hundred and three patients (79.84%) experienced disease recurrence, and 65 patients (50.39%) died. The median OS was 42.3 months (95% CI: 34.3–50.3), and the median PFS was 9.9 months (95% CI: 8.2–11.6). Compared to patients with a high number of NAC cycles, the patients with a low number of NAC cycles had better a PFS (P<0.001, mPFS: 13.3 *vs.* 6.0 months) and better OS (P=0.008, mOS: 57.7 *vs.* 32.1 months) (*Figure 3*).

Univariate analysis revealed that age ≤60 years, non-R0 resection, major liver resection, bilobar distribution, multiple metastases, node-positive primary tumour, >5 NAC cycles and targeted therapy were associated with a reduced PFS. Multivariate analysis showed that >5 NAC cycles (HR =1.808, 95% CI: 1.205–2.712, P=0.004) and node-positive primary tumours (HR =1.858, 95% CI: 1.204–2.868, P=0.005) were independently associated with a reduced PFS and R0 resection (HR =0.642, 95% CI:

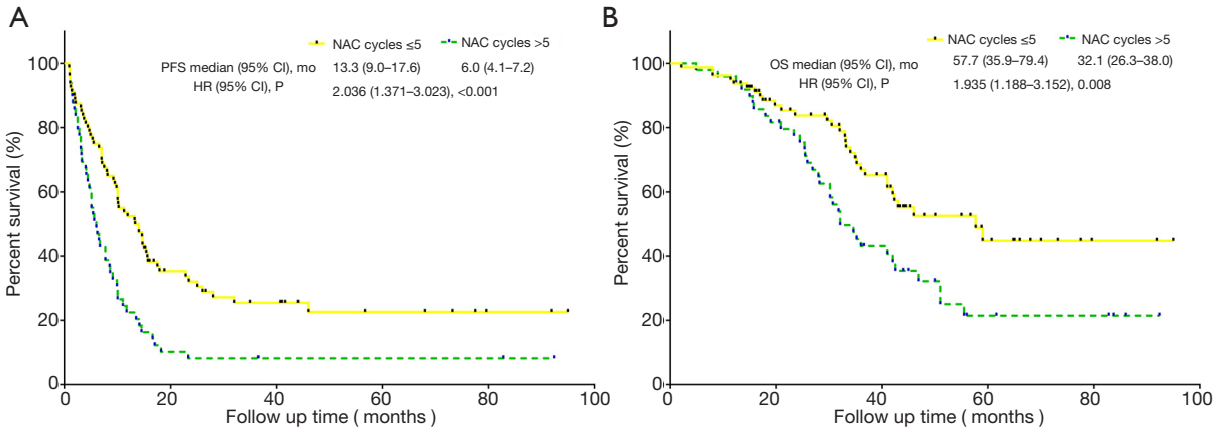

Figure 3 Survival analysis before propensity matching. (A) PFS analysis, (B) OS analysis. NAC, neoadjuvant chemotherapy; PFS, progression-free survival; OS, overall survival.

0.419–0.982, P=0.041) was an independent predictor of a prolonged PFS (*Table 2*).

Univariate analysis revealed that major liver resection, complications and >5 NAC cycles were associated with a reduced OS, and postoperative chemotherapy was associated with a prolonged OS. Multivariate analysis showed that bilobar distribution (HR =1.744, 95% CI: 1.039–2.928, P=0.035), complications (HR =2.207, 95% CI: 1.321–3.686, P=0.002) and >5 NAC cycles (HR =1.723, 95% CI: 1.041–2.851, P=0.034) were independent predictors of a reduced OS and postoperative chemotherapy (HR =0.557, 95% CI: 0.336–0.924, P=0.024) was an independent predictor of a prolonged OS (*Table 2*).

Subgroup analysis of different NAC regimens

Ninety-five patients received an oxaliplatin-based regimen. In the oxaliplatin-based regimen group, patients with a low number of NAC cycles had better PFS (P<0.001, mPFS: 14.7 *vs.* 5.4 months) and better OS (P=0.018, mOS: 57.7 *vs.* 41.0 months) than those with a higher number of NAC cycles (*Figure 4*). The number of patients receiving irinotecan-based regimens (15 cases) or oxaliplatin + irinotecan regimens (19 cases) was limited. Thus, a survival analysis could not be conducted.

After 1:1 propensity matching

Compared to patients with a high number of NAC cycles, the patients with a low number of NAC cycles had significantly better PFS (P<0.001, mPFS: 14.7 *vs.* 5.6 months) and better OS (P=0.012, mOS: 59.0 *vs.* 31.8 months) (*Figure 5*).

Univariate analysis revealed that ASA score 3-4, non-R0 resection, major liver resection, bilobar distribution, multiple metastases, node-positive primary tumour, >5 NAC cycles and targeted therapy were associated with a reduced PFS and postoperative chemotherapy was associated with a prolonged PFS. Multivariate analysis showed that bilobar distribution (HR =2.176, 95% CI: 1.203–3.935, P=0.010) and >5 NAC cycles (HR =2.265, 95% CI: 1.281–4.007, P=0.005) were independent predictors of a reduced PFS and postoperative chemotherapy (HR =0.517, 95% CI: 0.291–0.921, P=0.025) was an independent predictor of a prolonged PFS (*Table 3*).

Univariate analysis revealed that non-R0 resection, metastasis diameter ≥3 cm, node-positive primary tumour, NAC toxicity and >5 NAC cycles were associated with a reduced OS and postoperative chemotherapy was associated with a prolonged OS. Multivariate analysis showed that >5 NAC cycles (HR =2.813, 95% CI: 1.359–5.822, P=0.005) was an independent predictor of a reduced OS and postoperative chemotherapy (HR =0.312, 95% CI: 0.153–0.636, P=0.001) was an independent predictor of a prolonged OS (*Table 3*). The result that >5 NAC cycles was an independent predictor of a reduced PFS and reduced OS was consistent with the result before propensity matching.

Subgroup analysis in different NAC regiments

Fifty-two patients received oxaliplatin-based regimen. In the oxaliplatin-based regimen group, patients with a low number of NAC cycles had better PFS (P<0.001, mPFS: 17.5 *vs.* 5.6 months) and better OS (P=0.008, mOS: 59.0 *vs.* 31.8 months) (*Figure 6*). The number of patients receiving irinotecan-based regimen (6 cases) or oxaliplatin + irinotecan regimen (10 cases) was limited. Thus, a survival

Table 2 Univariate and multivariate analyses of predictive factors of PFS and OS for CLOM patients before propensity matching

Factor	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)
Age >60 years	0.045	0.652 (0.429–0.991)			0.672	0.894 (0.531–1.504)		
Male	0.951	0.988 (0.667–1.462)			0.614	0.939 (0.734–1.200)		
Preoperative CEA >10 ng/mL	0.489	1.149 (0.776–1.702)			0.581	1.148 (0.0.704–1.872)		
BMI >24 kg/m^2	0.874	1.033 (0.692–1.542)			0.764	0.925 (0.558–1.536)		
Comorbidity	0.901	1.025 (0.691–1.521)			0.333	0.779 (0.470–1.291)		
ASA score 3–4	0.249	1.395 (0.792–2.459)			0.505	0.786 (0.388–1.594)		
Synchronous metastasis	0.464	1.243 (0.694–2.225)			0.909	1.044 (0.498–2.191)		
Left hemicolon	0.842	1.061 (0.592–1.901)			0.123	1.708 (0.865–3.373)		
R0 resection	0.019	0.606 (0.398–0.921)	0.041	0.642 (0.419–0.982)	0.098	0.635 (0.370–1.087)		
Major liver resection	0.005	1.737 (1.176–2.565)			0.015	1.846 (1.129–3.018)		
Bilobar distribution	0.008	1.697 (1.149–2.506)			0.087	1.537 (0.940–2.512)	0.035	1.744 (1.039–2.928)
Diameter of metastases ≥3 cm	0.653	1.093 (0.742–1.611)			0.106	1.497 (0.918–2.442)		
Multiple metastases	0.013	1.733 (1.125–2.669)			0.419	1.243 (0.733–2.106)		
Complications	0.448	1.162 (0.789–1.710)			0.003	2.140 (1.305–3.501)	0.002	2.207 (1.321–3.686)
Poor differentiation	0.067	1.522 (0.971–2.385)			0.178	1.465 (0.840–2.555)		
T3-T4 stage	0.110	1.669 (0.891–3.126)			0.703	1.165 (0.531–2.559)		
Node-positive primary tumor	0.002	2.005 (1.301–3.089)	0.005	1.858 (1.204–2.868)	0.076	1.645 (0.949–2.850)		
NAC toxicity	0.397	0.830 (0.540–1.277)			0.475	1.248 (0.679–2.295)		
Neutropenia	0.604	0.900 (0.605–1.339)			0.602	1.142 (0.694–1.878)		
Heterochronous resection	0.537	0.871 (0.561–1.352)			0.166	0.832 (0.641–1.079)		
Preoperative chemotherapy								
Oxaliplatin based regimen	0.128	0.715 (0.464–1.101)			0.126	0.657 (0.384–1.125)		
NAC cycles >5	<0.001	2.036 (1.371–3.023)	0.004	1.808 (1.205–2.712)	0.008	1.935 (1.188–3.152)	0.034	1.723 (1.041–2.851)
Targeted therapy	0.002	1.905 (1.267–2.864)			0.118	1.498 (0.902–2.488)		
Pathological response	0.307	0.812 (0.544–1.211)			0.358	0.792 (0.481–1.303)		
Postoperative chemotherapy	0.132	0.741 (0.502–1.094)			0.004	0.488 (0.299–0.796)	0.024	0.557 (0.336–0.924)

PFS, progression-free survival; OS, overall survival; CLOM, colorectal liver oligometastases; NAC, neoadjuvant chemotherapy; CEA, carcinoembryonic antigen; BMI, body mass index; ASA, American society of anesthesiologists physical status classification.

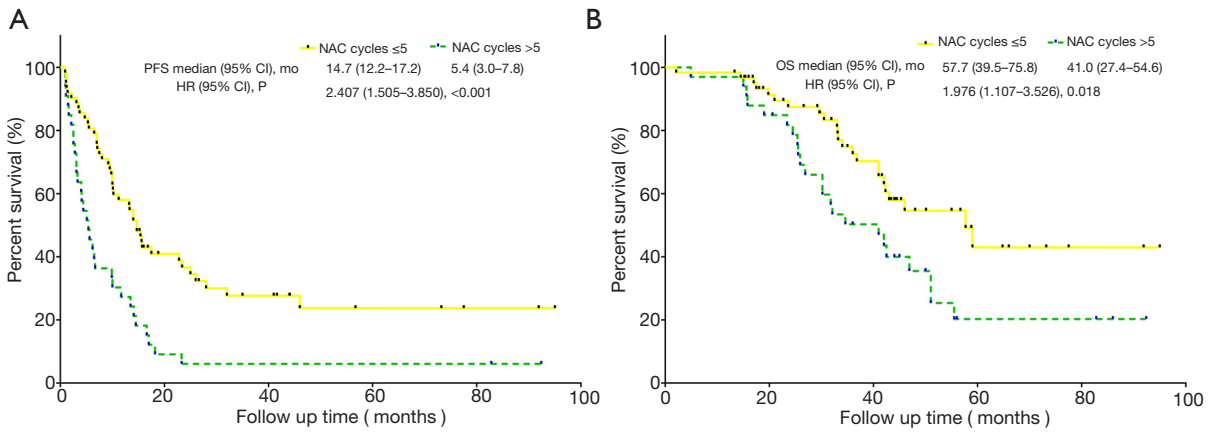

Figure 4 Survival analysis in patients receiving oxaliplatin-based regimen before propensity matching. (A) PFS analysis, (B) OS analysis. NAC, neoadjuvant chemotherapy; PFS, progression-free survival; OS, overall survival.

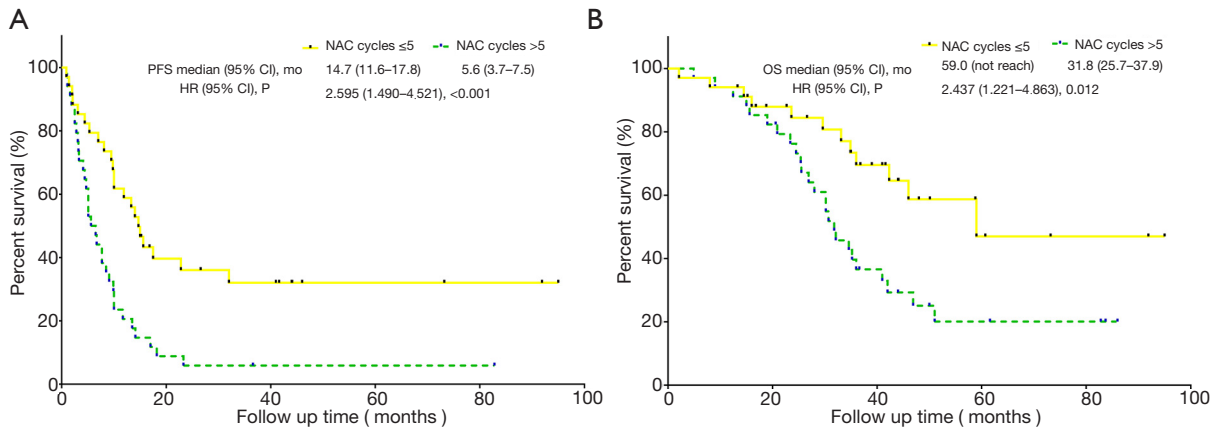

Figure 5 Survival analysis after propensity matching. (A) PFS analysis, (B) OS analysis. NAC, neoadjuvant chemotherapy; PFS, progression-free survival; OS, overall survival.

analysis could not be conducted.

Discussion

To the best of our knowledge, this study was the first to investigate the optimal number of NAC cycles for biologically resectable CLOM. X-tile analysis was used and determined that 5 was the optimal cut-off value for NAC cycles. The results of this study revealed that CLOM patients receiving ≤5 NAC cycles had favourable PFS and OS in the multivariate analysis. In a separate analysis of patients receiving an oxaliplatin-based regimen, the study yielded consistent results. A 1:1 propensity score matching analysis confirmed this finding. Thus, 5 NAC cycles represent an inflection point for resection with unfavourable outcomes.

For CRLM patients, the total number of liver metastases is an important factor for the choice of treatment strategies. Patients with more than five liver metastases were considered to have biological unresectable disease and were recommended to receive NAC (18). Patients with ≤5 CRLM, especially those without extrahepatic metastases, were regarded as a unique subgroup (CLOM) (6,7). CLOM is a relatively early stage of biological invasion between localized primary tumours and widespread metastatic tumours. Effective control of tumour progression at this stage can significantly improve the prognosis of patients. For biologically resectable CLOM, NAC is increasingly recommended because of its several potential advantages, including early elimination of distant micrometastases,

Table 3 Univariate and multivariate analyses of predictive factors of PFS and OS for CLOM patients after propensity matching

Factor	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95%CI)
Age >60 years	0.319	0.742 (0.413–1.334)			0.640	1.175 (0.597–2.315)		
Male	0.799	1.074 (0.621–1.858)			0.885	0.976 (0.699–1.362)		
Preoperative CEA >10 ng/mL	0.645	0.879 (0.509–1.518)			0.777	1.098 (0.575–2.097)		
BMI >24 kg/m^2	0.534	0.838 (0.478–1.469)			0.591	1.203 (0.613–2.362)		
Comorbidity	0.857	1.052 (0.605–1.831)			0.769	0.904 (0.460–1.777)		
ASA score 3–4	0.045	2.207 (1.016–4.792)			0.254	1.617 (0.708–3.690)		
Synchronous metastasis	0.964	1.017 (0.480–2.158)			0.669	1.255 (0.444–3.548)		
Left hemicolon	0.862	1.069 (0.502–2.278)			0.147	1.846 (0.806–4.229)		
R0 resection	0.049	0.549 (0.303–0.996)			0.006	0.366 (0.178–0.755)		
Major liver resection	0.016	2.032 (1.141–3.619)			0.079	1.862 (0.930–3.729)		
Bilobar distribution	0.002	2.519 (1.424–4.458)	0.010	2.176 (1.203–3.935)	0.085	1.825 (0.921–3.616)		
Diameter of metastases ≥3 cm	0.973	1.009 (0.588–1.732)			0.030	2.164 (1.078–4.345)		
Multiple metastases	0.030	2.792 (1.104–7.063)			0.529	1.396 (0.494–3.947)		
Complications	0.221	0.714 (0.416–1.224)			0.488	1.257 (0.658–2.404)		
Poor differentiation	0.174	1.511 (0.834–2.740)			0.084	1.865 (0.919–3.782)		
T3-T4	0.439	1.349 (0.633–2.875)			0.588	1.334 (0.470–3.789)		
Node-positive primary tumor	0.007	2.396 (1.267–4.530)			0.037	2.333 (1.050—5.184)		
NAC toxicity	0.196	0.605 (0.283–1.296)			0.044	0.400 (0.164–0.976)		
Neutropenia	0.581	0.858 (0.499–1.475)			0.811	0.923 (0.478–1.781)		
Heterochronous resection	0.304	0.730 (0.401–1.330)			0.704	0.932 (0.647–1.341)		
Preoperative chemotherapy								
Oxaliplatin based regimen	0.037	0.521 (0.282–0.960)			0.256	0.663 (0.327–1.347)		
NAC cycles >5	0.001	2.595 (1.490–4.521)	0.005	2.265 (1.281–4.007)	0.012	2.437 (1.221–4.863)	0.005	2.813 (1.359–5.822)
Targeted therapy	0.035	1.824 (1.044–3.185)			0.375	1.362 (0.688–2.700)		
Pathological response	0.393	0.785 (0.451–1.367)			0.257	0.676 (0.343–1.331)		
Postoperative chemotherapy	0.007	0.470 (0.271–0.813)	0.025	0.517 (0.291–0.921)	0.001	0.320 (0.165–0.621)	0.001	0.312 (0.153–0.636)

PFS, progression-free survival; OS, overall survival; CLOM, colorectal liver oligometastases; NAC, neoadjuvant chemotherapy; CEA, carcinoembryonic antigen; BMI, body mass index; ASA, American society of anesthesiologists physical status classification.

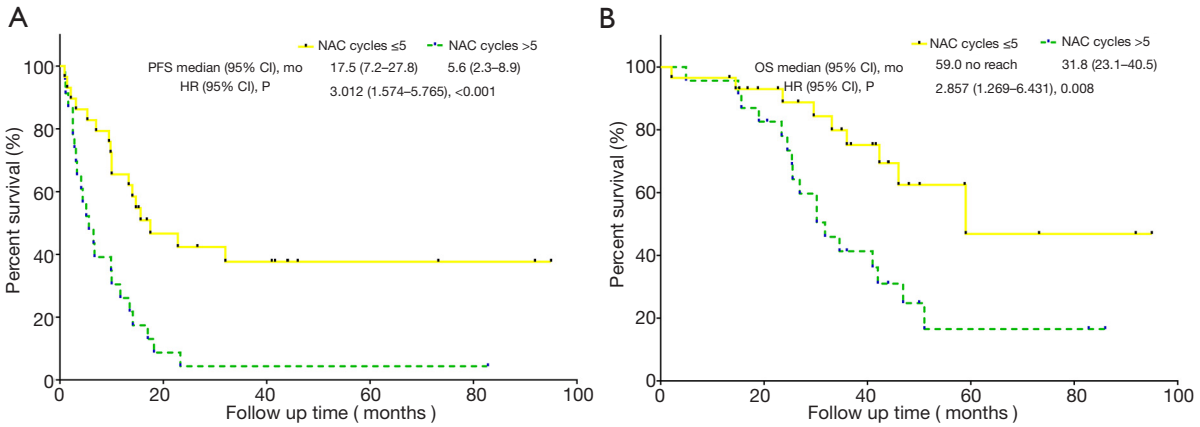

Figure 6 Survival analysis in patients receiving oxaliplatin-based regimen after propensity matching. (A) PFS analysis; (B) OS analysis. NAC, neoadjuvant chemotherapy; PFS, progression-free survival; OS, overall survival.

improved resectability that leads to survival benefits, and *in vivo* evaluation of chemotherapy regimen response (8). However, clinicians need to address an important question: what is the optimal number of NAC cycles for CLOM patients? For unresectable CRLM, the choice of the number of NAC cycles was determined to achieve resectability. Unlike that for unresectable CRLM, the number of NAC cycles for biologically resectable CLOM can be chosen objectively. However, an insufficient number of cycles of NAC cannot lead to the maximum benefits and realize the advantages of NAC. In contrast, an excessive number of NAC cycles may cause adverse effects such as impaired immune function, reduced sensitivity to chemotherapy regimens and an elevated risk of developing distant metastasis. It is necessary for us to investigate the optimal number of NAC cycles.

There is still no consensus on the number of NAC cycles for biologically resectable CLOM patients. The NCCN guidelines (11) recommend the option of NAC for resectable CRLM for a period of 2–3 months but do not specify how many cycles of NAC would benefit patients the most. This study implemented X-tile analyses to objectively identify the optimal number of NAC cycles for CLOM instead of arbitrarily determining the cut-off point of NAC cycles. Five NAC cycles for CLOM was the inflection point in survival, and >5 NAC cycles led to unfavourable survival. The mechanisms of this result may be as follows: (I) more NAC cycles would impair immune function and nutritional status (19,20), which is not conducive to the prognosis of patients (21). Some studies have shown that prolonging chemotherapy cycles leads to the occurrence of sarcopenia (22) and chemotherapy toxicities (12), and sarcopenia and NAC chemotherapy toxicities are significantly related to poor patient prognosis (13,23). (II) The sensitivity of the tumour to the chemotherapy regimen may decrease as the chemotherapy cycles are extended (24). Once chemotherapy regimens cannot completely control the tumour, the risk of local progression or metastasis increases and CRLM can even convert into unresectable liver metastasis. In addition, the reduction in tumour sensitivity to chemotherapy regimens would not be conducive to postoperative adjuvant chemotherapy and palliative chemotherapy after recurrence. (III) Prolonged chemotherapy cycles may lead to further reductions in the size of liver metastasis. There is the possibility that local metastatic tumours disappear and cannot be found by imaging (25); thus, these metastases cannot be completely removed by surgery. Some studies have shown that more than half of these metastases will recur *in situ* (26,27). (IV) A few preclinical studies have demonstrated that NAC may induce cancer metastasis through a tumour microenvironment of metastasis-mediated and/or extracellular vesicle-mediated mechanisms (28,29).

When investigating the optimal number of NAC cycles, the study has to consider the heterogenicity of NAC regimens. To address this bias, this study used a 1:1 propensity score matching analysis to balance the NAC regimen differences between the two groups. In addition, we conducted subgroup analyses according to different NAC regimens. Although the study did not conduct subgroup analyses according to all NAC regimens because of the limited sample size (oxaliplatin-based regimen: 95;

irinotecan-based regimen: 15 cases; oxaliplatin + irinotecan regimen: 19 cases), for patients receiving oxaliplatin-based regimen, the study yielded consistent results (patients who received ≤5 NAC cycles had favourable PFS and OS) before and after propensity score matching analysis.

It is important to note that our study revealed that additional NAC cycles not only did not change the R0 resection rate and pathological response rate but also increased the risk of NAC toxicity. In addition, additional NAC cycles may increase the risk of perioperative bleeding due to increased tissue fragility and inflammatory response (30). In conclusion, we do not recommend NAC for more than five cycles.

There are several limitations in this study. First, this was a retrospective, single-institution study with a small sample size. Selection bias was inevitable and may have influenced our results. Second, the number of NAC cycles was determined by the MDT team, which had bias for outcome. In order to decrease the selection bias, the propensity score matching was performed in this study. There is no doubt that propensity score matching can decrease the selection bias but does not eliminate it and decrease the numbers eligible for analyses, which was the limitation of this study. Third, there is still a lack of high-level clinical evidence on whether CRLM patients should receive postoperative chemotherapy and on the optimal cycles of postoperative chemotherapy. The differences of postoperative chemotherapy in this study lead to the survival bias. Last, this study did not include the KRAS status in the analysis because only 76 patients had available KRAS statuses. Despite these limitations, we believe that our study results may provide valuable applicable information to routine clinical practice.

In conclusion, our retrospective analysis showed that fewer than 5 NAC cycles was optimal for biologically resectable CLOM patients. Giving more than 5 cycles of NAC was unnecessary because a higher number of NAC cycles leads to more unfavourable survival and increased NAC toxicity while leading to similar R0 resection rates and pathological response rates. Our findings should be confirmed by prospective and controlled trials.

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Footnote

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Ethics Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All participants gave informed consent before taking part in this study. This study was conducted with approval from the Institute Research Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences (ID:NCC2019C-016). The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

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