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ORIGINAL ARTICLE

Neo-adjuvant Chemotherapy-Induced Neutropenia Is Associated with Histological Responses and Outcomes after the Resection of Colorectal Liver Metastases

Qichen Chen[1] · Chaorui Wu[2] · Hong Zhao[1] · Jianxiong Wu[1] · Jianjun Zhao[1] · Xinyu Bi[1] · Zhiyu Li[1] · Zhen Huang[1] · Yefan Zhang[1] · Jianguo Zhou[1] · Jianqiang Cai[1]

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Abstract

Background Neutropenia, the major adverse event in chemotherapy, is associated with favourable clinical outcome in several solid tumours. We aimed to investigate the predictive value of neo-adjuvant chemotherapy (NAC)–induced neutropenia for the pathological response and prognosis in colorectal liver metastases (CRLM) patients.

Methods A retrospective review was performed in 141 CRLM patients receiving NAC followed by liver resection. A logistic regression was applied to analyse potential predictors. A Cox proportional hazards analysis was used to analyse survival.

Results Neutropenia due to NAC was observed in 42.6% (60/141) of all patients, and grade 3/4 neutropenia was noted in 31.7% (19/60). A pathological response (tumour regression grade (TRG) 1–3) was reported in 46.1% (65/141) of patients. Multivariate analysis showed that neutropenia significantly predicted the favourable pathological response (OR = 3.718, 95% CI 1.716–8.329, $P = 0.001$), as well as targeted therapy, good differentiation and preoperative CEA < 10 ng/ml as independent predictors of favourable histological response. Of the patients, 54.6% (77/141) had postoperative complications, including 28 major complications (28/77, 36.4%). Severe neutropenia significantly predicted postoperative major complications in multivariate analysis (OR = 4.077, 95% CI 1.184–14.038, $P = 0.026$). Compared to patients without neutropenia, patients with neutropenia had significantly better progression-free survival (PFS) ($P = 0.007$; mPFS, 10.2 months vs. 6.7 months). Patients with histological response had significantly better PFS than patients with no histological response ($P = 0.001$; mPFS, 10.0 months vs. 5.5 months). According to multivariate analyses, neutropenia was a significant predictor for better PFS (HR = 0.613, 95% CI 0.406–0.925, $P = 0.020$) but not OS.

Conclusions For CRLM patients receiving NAC followed by liver resection, NAC-induced neutropenia was a significant predictor of favourable pathological response, postoperative major complications and better prognosis, which makes it useful for CRLM patients in guiding treatment approaches and prognosis assessments.

Keywords Colorectal cancer liver metastasis · Liver resection · Neo-adjuvant chemotherapy · Neutropenia · Histological response · Prognosis

Qichen Chen and Chaorui Wu contributed equally to this work.

✉ Jianguo Zhou
zjgty@hotmail.com

[1] Department of Hepatobiliary Surgery, National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

[2] Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Introduction

Colorectal cancer is the third most common cancer and the third leading cause of cancer-related deaths worldwide.[1] Approximately 50% of patients develop liver metastases during the course of colorectal cancer.[2] Surgical liver resection is the most effective treatment for colorectal liver metastases (CRLM) and is currently the only potentially curative therapeutic option.[3,4] Neo-adjuvant chemotherapy (NAC) has been advocated in patients with initially resectable and unresectable CRLM,[5–7] which improves survival by treating micro-metastases, down-staging the disease and increasing the resection

rate.[6] However, a pathological response, an important prognostic factor for chemotherapy efficacy, was reported in only 45–57% of these patients.[8–10] Postoperative complications have a reported prevalence of 4–53%,[11,12] and more than 70% of patients will have a recurrence after resection for CRLM.[13] Therefore, it is crucial to increase the ability to predict the outcomes for CRLM patients receiving NAC followed by liver resection to help select eligible patients for preoperative chemotherapy and liver resection.

Neutropenia, the major adverse event in chemotherapy, has been suggested as a prognostic factor predicting better clinical outcome in several solid tumours, such as non-small cell lung cancer,[14] colorectal cancer,[15,16] gastric cancer,[17] breast cancer,[18] cervical cancer,[19] nasopharyngeal cancer[20] and haematological malignancies.[21,22] However, these studies only focus on patients with advanced cancer receiving chemotherapy. The predictive (i.e. estimation from chemotherapy) or prognostic (i.e. estimation of the chance of survival) role of neutropenia in CRLM patients receiving NAC followed by liver resection has not been established. On the other hand, recent studies[23–26] have shown that severe chemotoxicity including neutropenia in patients with gastric cancer receiving NAC is closely related to the occurrence of postoperative major complications.

Therefore, we hypothesised that neutropenia might be related to an increased response to preoperative chemotherapy, postoperative major complications and better surgical prognosis in CRLM. To address this, we analysed the neutropenia due to NAC in our series of CRLM patients.

Materials and Methods

Patients and Treatment

We retrospectively collected 141 diagnosed CRLM patients receiving NAC followed by liver resection from December 2007 to December 2016 in our hospital. This study was approved by the Institutional Review Board of the Cancer Institute and Hospital, Chinese Academy of Medical Sciences. All patients provided written informed consent.

The treatment strategies for CRLM were discussed by a multidisciplinary team (MDT), including surgeons, oncologists and radiologists. Patients with multiple high-risk factors[25,26] or initially unresectable liver metastases were recommended to receive NAC. NAC was administered according to a protocol mainly comprised of a combination of 5-fluorouracil/capecitabine and oxaliplatin/irinotecan, with or without bevacizumab and cetuximab. Targeted therapy included bevacizumab and cetuximab. NAC toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.0).[27] A complete blood cell count was performed biweekly during the first cycle and monthly during and after the second cycle. A neutrophil count < 3000/μl was defined as indicating neutropenia. Those in the ranges of 1500–2999/μl, 1000–1499/μl, 500–999/μl and < 500/μl were classified as grades 1, 2, 3 and 4 neutropenia, respectively. Neutropenia grade 3–4 was defined as severe neutropenia. Patients with grade 3–4 neutropenia were administered granulocyte-colony stimulating factor (G-CSF) according to established guidelines. The clinical response to NAC was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST).[28] A clinical response was defined as either complete response (CR) or partial response (PR), and a non-response was defined as either stable disease (SD) or progressive disease (PD).

All patients received liver resections, usually within 4–6 weeks after the completion of NAC. Major resections were defined as resections of more than two segments, and other resections were described as being minor resections. R0 resection was defined as no viable tumour cells < 1 mm from the resection margin. Patients who met the following criteria were generally recommended intraoperative RFA: the number of lesions did not exceed 4 and the maximum diameter ≤ 3 cm; lesions were not localised superficially; lesions were located more deeply or proximal to major vascular structures, vulnerable structures (e.g. colon, stomach) or major bile ducts. The postoperative adjuvant chemotherapy was delivered based on NAC, pathological response and margin status.

The pathological response in this study was evaluated on lesions obtained through liver resection. The highest the tumour regression grade (TRG) for each patient with multiple metastases was used. The pathological responses to NAC were evaluated according to TRG as follows[29]: grade 1—the absence of tumour cells replaced by abundant fibrosis; grade 2—rare residual tumour cells scattered throughout abundant fibrosis; grade 3—more residual tumour cells throughout the predominant fibrosis; grade 4—a large number of tumour cells predominating over fibrosis; grade 5—the almost exclusive presence of tumour cells without fibrosis. Histological TRG 1–3 was defined as a favourable response to NAC.

Follow-Up and Outcomes

Patients were followed up with contrast-enhanced CT and/or MRI at 3-month intervals for up to 2 years and every 6 months thereafter. The outcomes include short-term outcome (postoperative complications) and long-term outcome (overall survival and progression-free survival). Each postoperative complication was allocated a severity grade using the Clavien–Dindo classification system,[30] and major complications were classified as Clavien–Dindo III–V. If multiple morbidities occurred in one patient, the higher grade was used. Progression-free survival (PFS) was defined from the date of surgery to the date of the first recurrence or progression of the (residual)

disease. Overall survival (OS) was defined from the date of surgery to the date of death.

Statistical Analysis

Comparisons between continuous variables were made using non-parametric Mann–Whitney *U* tests. The categorical variables were compared using Fisher's exact tests. A ROC curve was constructed to estimate the optimal cut-off value of the operation time and blood loss during surgery. The median OS and PFS were determined with a Kaplan–Meier analysis, and the differences between the two groups were assessed using the log-rank test. All predictors with $P < 0.10$ by univariate analysis were retained in the multivariate models. Multivariate analyses of OS and PFS were performed using Cox regression models. To prevent colinearity, when two variables were significantly correlated, we included A variable into multivariate model 1 and B variable into multivariate model 2, respectively. All statistical analyses were considered significant at $P < 0.05$. Statistical analyses were performed using SPSS, version 22 software (Armonk, NY, USA).

Results

Patient and Tumour Characteristics

A total of 141 patients, 92 male (65.2%) and 49 female (34.8%), met the inclusion criteria for this study. The median age at liver resection was 55 (interquartile range (IQR) 49.0–62.0) years. The median BMI was 24.3 (IQR 22.6–26.4) kg/m^2. Moreover, 43.3% (61/141) of patients had comorbidities (diabetes—23, 37.7%; hypertension—35, 57.4%; cardiac disease—7, 11.5%; others—8, 13.1%). ASA score 1–2 was noted in 87.2% of the patients. Most patients (85.1%) developed synchronous liver metastases. The primary sites were located in the colon in 74 patients (52.5%). The median diameter of the largest lesion was 2.8 (IQR 1.8–4.0) cm, and 48.2% of patients had a lesion larger than 3 cm. Of the patients, 70.2% had more than one metastasis, with a median of 3 (IQR 1.0–4.5) lesions. A bilobar distribution of metastases was observed in 48.2% of the patients. Poor differentiation was observed in 23.6% of the patients.

Ninety-four patients (66.7%) received an oxaliplatin regimen. Forty-eight patients (34.0%) received targeted therapy, including 21 patients receiving bevacizumab therapy, 26 patients receiving cetuximab therapy and 1 patient receiving bevacizumab combined with cetuximab therapy. The median number of NAC cycles was 5, with 43 (30.5%) patients receiving more than 6 cycles and 19 patients (13.6%) receiving second-line chemotherapy. NAC toxicities were observed in 122 (86.5%) patients. Fifty-nine patients had haematologic toxicities and 106 had non-haematologic toxicities. Neutropenia due to NAC was observed in 42.6% (60/141), and grade 3/4 neutropenia (severe neutropenia) was noted in 31.7% (19/60). No mortality was observed due to NAC. Seventy seven patients (56.2%) achieved a clinical response after NAC. A favourable pathological response was reported in 65 (46.1%) of 141 patients, including a complete response in 1 patient and a partial response (TRG 2–3) in 64 patients. Ninety patients (63.8%) had R0 resection at pathological evaluation (Table 1).

Major liver resection, laparoscopic liver resection and heterochronous resection were observed in 53.9%, 30.5% and 29.1% of the patients, respectively. Major liver resection with synchronous colon or rectal resection and minor liver resection with heterochronous colon or rectal resection were noted in 39.0% and 14.2% of the patients, respectively. The median operation time, median blood loss during surgery and percentage of blood transfusion was 340 (IQR 250.5–431.6) min, 300 (IQR 100–500) ml and 24.1% in all patients, respectively. Eighty one patients (57.4%) received postoperative adjuvant chemotherapy. The median time from operation to initiation of adjuvant chemotherapy was 40 (IQR 32.5–48.5) days. In patients receiving adjuvant chemotherapy, 39 patients (48.1%) had postoperative complications including 16 major complications and 23 minor complications. Adjuvant chemotherapy was noted in 57.1% (16/28) of patients with postoperative major complications and the rate of adjuvant chemotherapy was not significantly different between patients with major complications and patients without major complications ($P = 0.971$).

Relationship Between Neutropenia and Histological Response

Baseline clinicopathological characteristics based on NAC-induced neutropenia are summarised in Table 1. The two groups had mostly similar characteristics. The relationships between histological response and clinicopathological features are shown in Table 2. Univariate analysis revealed that the preoperative CEA ($P = 0.049$), type of differentiation ($P = 0.001$), targeted therapy ($P = 0.005$), clinical response ($P = 0.037$) and neutropenia ($P < 0.001$) all correlate with histological response. Multivariate analysis showed that neutropenia (OR = 3.718, 95% CI 1.716–8.329, $P = 0.001$) significantly predicted the favourable pathological response, as well as targeted therapy (OR = 2.656, 95% CI 1.175–6.002, $P = 0.019$), well/moderate differentiation (OR = 4.087, 95% CI 1.594–10.482, $P = 0.003$) and preoperative CEA <10 ng/ml (OR = 2.326, 95% CI 1.051–5.148, $P = 0.037$) as independent predictors of the favourable histological response.

Relationship Between Neutropenia and Postoperative Major Complications

In this study, 54.6% (77/141) of patients had postoperative complications, including 28 major complications (28/77,

Table 1 Patient and tumour characteristics

Item	No neutropenia ($n = 81$)	Neutropenia ($n = 60$)	P value	All patients ($n = 141$)
Age ≥ 60 years, *n* (%)	29 (35.8)	20 (33.3)	0.761	49 (34.8)
Female, *n* (%)	24 (29.6)	25 (41.7)	0.138	49 (34.8)
BMI > 24 kg/m^2, *n* (%)	45 (55.6)	29 (48.3)	0.396	74 (52.5)
Comorbidity, *n* (%)	44 (54.3)	17 (28.3)	0.002	61 (43.3)
ASA score 3–4, *n* (%)	12 (14.8)	6 (10.0)	0.397	18 (12.8)
Preoperative CEA ≥10 ng/ml, *n* (%)	32 (39.5)	26 (43.3)	0.648	58 (41.1)
Synchronous metastasis, *n* (%)	70 (86.4)	50 (83.3)	0.611	120 (85.1)
Primary site colon, *n* (%)	37 (45.7)	37 (61.7)	0.060	74 (52.5)
Left hemicolon, *n* (%)	9 (11.1)	8 (13.3)	0.689	17 (12.1)
R0 resection, *n* (%)	44 (54.3)	46 (76.7)	0.006	90 (63.8)
Major liver resection, *n* (%)	44 (54.3)	32 (53.3)	0.907	76 (53.9)
Heterochronous resection, *n* (%)	28 (34.6)	13 (21.7)	0.095	41 (29.1)
Minor liver resection with synchronous colon or rectal resection, *n* (%)	23 (28.4)	22 (36.7)	0.40	45 (31.9)
Minor liver resection with heterochronous colon or rectal resection, *n* (%)	14 (17.3)	6 (10.0)		20 (14.2)
Major liver resection with synchronous colon or rectal resection, *n* (%)	30 (37.0)	25 (41.7)		55 (39.0)
Major liver resection with heterochronous colon or rectal resection, *n* (%)	14 (17.3)	7 (11.7)		21 (14.9)
Concomitant RFA, *n* (%)	19 (23.5)	11 (18.3)	0.462	30 (21.3)
Bilobar distribution, *n* (%)	45 (55.6)	23 (38.3)	0.043	68 (48.2)
Extrahepatic metastases, *n* (%)	9 (11.1)	8 (13.3)	0.689	17 (12.1)
Diameter of metastases ≥ 3 cm, *n* (%)	39 (48.1)	29 (48.3)	0.983	68 (48.2)
Multiple metastases, *n* (%)	60 (74.1)	39 (65.0)	0.244	99 (70.2)
Operation time (min), median (IQR)	340.0 (243.8–446.0)	344.3 (250.5–423.8)	0.980	340.0 (250.5–431.6)
Blood loss (ml), median (IQR)	200 (100.0–500.0)	300 (125.0–500)	0.354	300.0 (100.0–500.0)
Blood transfusion, *n* (%)	19 (23.5)	15 (25.0)	0.832	34 (24.1)
Laparoscopic liver resection, *n* (%)	21 (25.9)	22 (36.7)	0.171	43 (30.5)
Poorly differentiated, *n* (%)	27 (23.3)	42 (23.9)	0.908	69 (23.6)
T3–T4, *n* (%)	13 (11.2)	36 (20.5)	0.039	49 (16.8)
KRAS mutation, *n* (%)[a]	13 (24.1)	14 (34.1)	0.281	27 (28.4)
Preoperative chemotherapy				
Oxaliplatin, *n* (%)	56 (69.1)	38 (63.3)	0.447	94 (66.7)
Irinotecan, *n* (%)	14 (17.3)	9 (15.0)		23 (16.3)
Oxaliplatin + irinotecan, *n* (%)	11 (13.6)	13 (21.7)		24 (17.0)
Cycles > 6, *n* (%)	22 (27.2)	21 (35.0)	0.317	43 (30.5)
Targeted therapy, *n* (%)	26 (32.1)	22 (36.7)	0.571	48 (34.0)
Second-line chemotherapy, *n* (%)	10 (12.3)	9 (15.3)	0.620	19 (13.6)
Clinical response, *n* (%)	45 (57.0)	32 (55.2)	0.835	77 (56.2)
Pathological response, *n* (%)	26 (32.1)	39 (65.0)	< 0.001	65 (46.1)
Postoperative complications, *n* (%)	41 (50.6)	36 (60.0)	0.269	77 (54.6)
Postoperative major complications, *n* (%)	12 (14.8)	16 (26.7)	0.081	28 (19.9)
Adjuvant chemotherapy, *n* (%)	49 (60.5)	32 (53.3)	0.395	81 (57.4)

[a] KRAS status was available in 95 patients

36.4%) (surgery-related complications—9/28, 32.1%; general complications—19, 19/28, 67.9%) and 49 minor complications (63.6%). ROC curves illustrating the ability of the operation time and blood loss during surgery to predict postoperative major complications were performed. For operation time, the optimal cut-off level was 487 min. For blood loss, the optimal cut-off level was 250 ml. The relationships between major complications and clinicopathological features are shown in

Table 2 Prognostic factors for the pathological response in patients who underwent preoperative chemotherapy

Factor	Univariate analysis	Multivariate analysis	
	P value	OR (95% CI)	*P* value
Age ≥ 60 years	0.392		
Female	0.835		
BMI > 24 kg/m^2	0.475		
Comorbidity	0.967		
ASA score 3–4	0.880		
Preoperative CEA < 10 ng/ml	0.049	2.326 (1.051–5.148)	0.037
Synchronous metastasis	0.271		
Primary site colon	0.523		
Left hemicolon	0.101		
Bilobar distribution	0.142		
Extrahepatic metastases	0.933		
Diameter of metastases ≥ 3 cm	0.427		
Solitary metastases	0.087		
Well + moderate differentiation	0.001	4.087 (1.594–10.482)	0.003
T3–T4	0.130		
Preoperative chemotherapy			
Oxaliplatin-based regimen	0.500		
Cycles > 6	0.504		
Targeted therapy	0.005	2.656 (1.175–6.002)	0.019
Second-line chemotherapy	0.404		
Neutropenia	< 0.001	3.718 (1.716–8.329)	0.001
Clinical response	0.037		

Table 3. Univariate analysis revealed that diameter of metastases ($P = 0.020$), blood loss ($P = 0.008$), blood transfusion ($P = 0.010$) and severe neutropenia ($P = 0.009$) correlate with major complications. Multivariate analyses showed that severe neutropenia (OR = 4.077, 95% CI 1.184–14.038, $P = 0.026$) significantly predicted major complications, as well as operation time ≥ 487 min (OR = 3.580, 95% CI 1.110–11.548, $P = 0.003$) and blood transfusion (OR = 3.906, 95% CI 1.462–10.436, $P = 0.007$) as independent predictors of major complications.

Impact of Neutropenia and Histological Responses on Survival

The median follow-up was 25.2 months. At the time of analysis, 107 (75.9%) patients experienced disease recurrence, and 50 (34.5%) died. The median OS was 42.5 months (95% CI 32.0–53.0), and the median PFS was 7.9 months (95% CI 5.6–10.2). The 1-, 3- and 5-year survival rates were 92.9%, 54.1% and 36.4%, respectively. The 1- and 3-year PFS rates were 34.8% and 20.9%, respectively. The median PFS was 10.2 months (95% CI 7.3–13.1) in patients with neutropenia and 6.7 months (95% CI 4.9–8.5) in those with non-neutropenia ($P = 0.007$) (Fig. 1). The median OS was 42.3 months (95% CI 27.2–32.5) in the neutropenia group and 42.5 months (95% CI 32.5–52.5) in those without neutropenia ($P = 0.266$). The median PFS was 10.0 months (95% CI 5.7–14.3) in patients with favourable histological response and 5.5 months (95% CI 3.4–7.6) in those with unfavourable histological response ($P = 0.001$) (Fig. 2). The median OS was 44.2 months (95% CI 24.5–63.9) in those with favourable histological response and 42.3 months (95% CI 31.9–52.7) in those with unfavourable histological response ($P = 0.378$).

ROC curves were constructed to estimate the optimal cut-off value of the operation time and blood loss during surgery for predicting survival. For operation time, the optimal cut-off level was 347 min. For blood loss, the optimal cut-off level was 250 ml. The time from operation to initiation of adjuvant chemotherapy was significantly different between patients with postoperative major complications and those without ($P = 0.013$, median time 39 (IQR 32.0–45.0) days vs. 50.5 (IQR 35.0–67.8) days). The adjuvant chemotherapy was delayed by postoperative major complications. In order to answer whether the delayed adjuvant chemotherapy affected outcomes, we divided patients receiving adjuvant chemotherapy into delayed group and no delayed group according to the cut-off 40 days (the median time from operation to the initiation of adjuvant chemotherapy). Compared with no delayed group, delayed group has the equivalent OS and PFS

Table 3 Prognostic factors for major complications in CRLM patients after liver resection

Factor	Univariate analysis	Multivariate analysis	
	P value	OR (95% CI)	*P* value
Age ≥ 60 years	0.905		
Female	0.905		
BMI > 24 kg/m^2	0.118		
Comorbidity	0.185		
ASA score 3–4	0.716		
Preoperative CEA ≥ 10 ng/ml	0.131		
Synchronous metastasis	0.093		
Primary site colon	0.897		
Left hemicolon	0.686		
R0 resection	0.411		
Major liver resection	0.098		
Major liver resection with synchronous colon or rectal resection	0.060		
Concomitant RFA	0.982		
Bilobar distribution	0.832		
Extrahepatic metastases	0.686		
Diameter of metastases ≥ 3 cm	0.020		
Solitary metastases	0.280		
Operation time ≥ 487 min[a]	0.095	3.580 (1.110–11.548)	0.033
Blood loss ≥ 250 ml[a]	0.008		
Blood transfusion	0.010	3.906 (1.462–10.436)	0.007
Laparoscopic liver resection	0.805		
Poorly differentiated	0.578		
T3–T4	0.407		
Heterochronous resection	0.388		
Preoperative chemotherapy			
Oxaliplatin-based regimen	0.984		
Cycles > 6	0.259		
Targeted therapy	0.835		
Second-line chemotherapy	0.037		
Neutropenia	0.081		
Severe neutropenia	0.009	4.077 (1.184–14.038)	0.026
Clinical response	0.169		
Pathological response	0.376		

[a] ROC curves illustrating the ability of the operation time and blood loss during surgery to predict postoperative major complications were performed. For operation time, the optimal cut-off level was 487 min. For blood loss, the optimal cut-off level was 250 ml

(*P* = 0.317, mOS 42.3 months vs. 51.0 months; *P* = 0.532, mPFS 7.5 months vs. 10.0 months).

Univariate analysis revealed that histological response, clinical response, neutropenia, NAC cycles ≤ 6, R0 resection, solitary liver metastasis, no postoperative complication and minor resection were associated with increased PFS. Table 2 shows that neutropenia was significantly associated with pathological response in multivariate analysis. To prevent colinearity, neutropenia and pathological response were included in the multivariate analyses of model 1 and model 2, respectively. In a multivariate analysis of model 1, neutropenia (HR = 0.613, 95% CI 0.406–0.925, *P* = 0.020), favourable clinical response (HR = 0.547, 95% CI 0.361–0.829, *P* = 0.004), operation time < 347 min (HR = 0.652, 95% CI 0.432–0.984, *P* = 0.042) and solitary liver metastasis (HR = 0.502, 95% CI 0.314–0.804, *P* = 0.004) remained significant for a better PFS. In a multivariate analysis of model 2, favourable histological response (HR = 0.575, 95% CI 0.384–0.862, *P* = 0.007) and separate liver metastasis (HR = 0.501, 95% CI 0.314–0.800, *P* = 0.004) remained significant for a better PFS (Table 4).

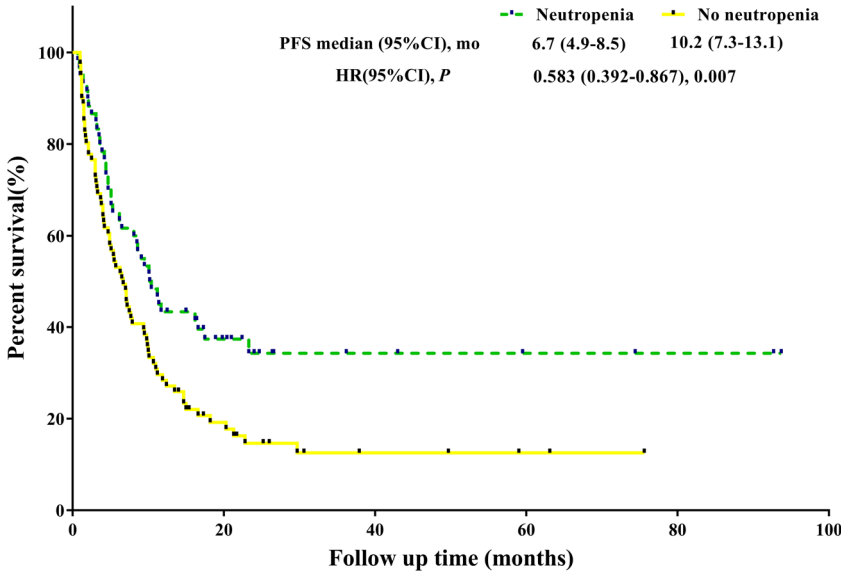

Fig. 1 PFS analysis of neutropenia versus no neutropenia

Univariate analysis and multivariate analysis revealed that neutropenia was not an independent predictor of OS. Multivariate analysis revealed that postoperative complications (HR = 2.124, 95% CI 1.143–3.948, $P = 0.017$), R1 resection, bilobar distribution, BMI > 24 kg/m^2 and no postoperative adjuvant chemotherapy are independently predictive factors for unfavourable OS (Table 5).

Discussion

To the best of our knowledge, this is the first study to investigate the relationship between NAC-induced neutropenia and the pathological responses of NAC and outcomes after CRLM resection. The results of our study revealed that NAC-induced neutropenia is associated with favourable pathological responses and a better PFS after liver resection. We also noted that severe neutropenia was correlated with postoperative major complications. These results might aid in selecting patients with CRLM for treatment strategies.

For CRLM patients receiving NAC, it is essential to achieve a favourable tumour response and downstaging with neo-adjuvant chemotherapy in order to improve the complete resection rate and prolong survival. Identifying factors with predictive ability in pathological responses during NAC have clinical utility, as they may provide information about the efficacy of NAC to adjust the treatment strategies. Recent studies reported that chemotherapy-induced neutropenia is a prognostic factor predicting better clinical outcome in many solid tumours,[17–21] many of which suggested that neutropenia was a signal of the efficacy of chemotherapy. However, there is still a lack of direct evidence to confirm this conclusion. At

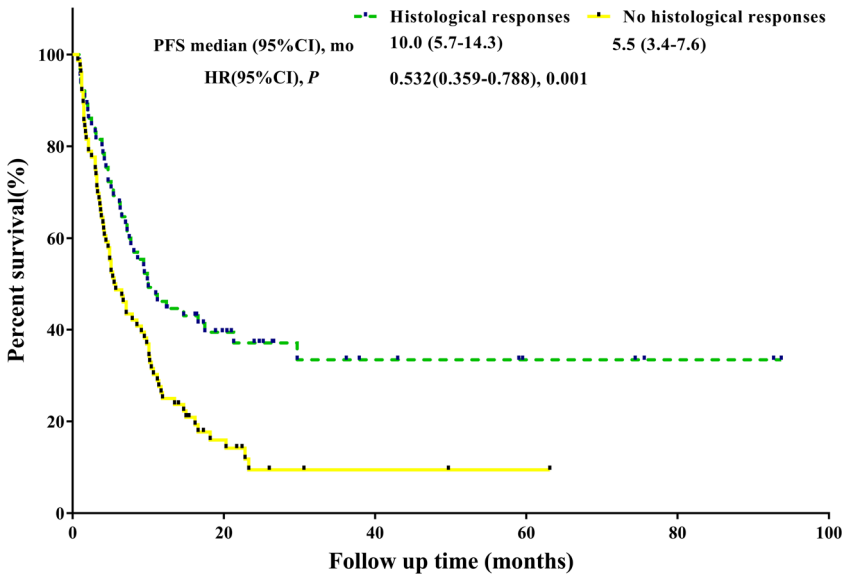

Fig. 2 PFS analysis of histological response versus no histological response

Table 4 Univariate and multivariate analyses of factors predictive of PFS for CRLM patients after liver resection

Factor	Univariate analysis		Multivariate analysis[a]			
			Model 1		Model 2	
	P value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)
Age ≥ 60 years	0.241	0.784 (0.522–1.178)				
Female	0.672	0.917 (0.614–1.370)				
Preoperative CEA ≥ 10 ng/ml	0.095	1.386 (0.945–2.033)				
BMI > 24 kg/m^2	0.365	1.192 (0.815–1.744)				
Comorbidity	0.644	1.094 (0.747–1.601)				
ASA score 3–4	0.569	1.172 (0.679–2.025)				
Synchronous metastasis	0.816	1.065 (0.626–1.813)				
Primary site colon	0.990	1.003 (0.685–1.467)				
Left hemicolon	0.635	0.864 (0.474–1.577)				
R0 resection	0.012	0.607 (0.412–0.894)				
Major liver resection	0.024	1.559 (1.061–2.292)				
Concomitant RFA	0.065	1.519 (0.975–2.367)				
Bilobar distribution	0.008	1.683 (1.146–2.470)				
Extrahepatic metastases	0.458	0.796 (0.436–1.453)				
Diameter of metastases ≥ 3 cm	0.816	0.956 (0.653–1.399)				
Solitary metastases	0.001	0.470 (0.299–0.739)	0.004	0.502 (0.314–0.804)	0.004	0.501 (0.314–0.800)
Operation time < 347min[b]	0.082	0.712 (0.486–1.044)	0.042	0.652 (0.432–0.984)		
Blood loss ≥ 550 ml[b]	0.823	0.943 (0.566–1.572)				
Blood transfusion	0.720	1.085 (0.693–1.699)				
Laparoscopic liver resection	0.517	1.144 (0.761–1.720)				
Postoperative complications	0.038	1.876 (1.035–3.400)				
Poorly differentiated	0.281	1.262 (0.827–1.928)				
T3–T4	0.299	1.264 (0.812–1.969)				
Heterochronous resection	0.783	1.060 (0.700–1.605)				
Preoperative chemotherapy						
Oxaliplatin-based regimen	0.488	0.839 (0.510–1.378)				
Cycles > 6	0.023	1.599 (1.068–2.393)				
Targeted therapy	0.246	1.263 (0.851–1.873)				
Second-line chemotherapy	0.250	1.366 (0.802–2.326)				
Neutropenia	0.008	0.583 (0.392–0.867)	0.020	0.613 (0.406–0.925)		
Clinical response	0.035	0.660 (0.448–0.972)	0.004	0.547 (0.361–0.829)		
Pathological response	0.002	0.532 (0.359–0.788)			0.007	0.575 (0.384–0.862)
Adjuvant chemotherapy	0.147	0.754 (0.515–1.105)				

[a] Multivariate analysis: Table 2 shows that neutropenia was significantly associated with pathological response in multivariate analysis. To prevent colinearity, neutropenia was included in the multivariate analysis of model 1 and pathological response was included in the multivariate analysis of model 2, respectively

[b] ROC curves were constructed to estimate the optimal cut-off value of the operation time and blood loss during surgery for predicting survival. For operation time, the optimal cut-off level was 347 min. For blood loss, the optimal cut-off level was 250 ml

present, pathological response is an important prognostic factor to evaluate the efficacy of chemotherapy. Most patients included in these studies were advanced and lost the opportunity to receive resection to evaluate pathological response, so the relationship between neutropenia and pathological response remains unclear. This study included patients receiving NAC followed by liver resection to evaluate pathological response. Our results show that neutropenia was associated with favourable pathological responses for CRLM patients receiving NAC. The possible mechanism is as follows: chemotherapy regimens, including oxaliplatin and irinotecan, can not only destroy cancer tissue but also result in serious damage to the normal tissue of the host. Some studies show that haematotoxicity in the host and the pathological response in

Table 5 Univariate and multivariate analyses of factors predictive of OS for CRLM patients after liver resection

Factor	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	*P* value	HR (95% CI)
Age ≥ 60 years	0.446	0.786 (0.424–1.459)		
Female	0.965	1.013 (0.571–1.796)		
Preoperative CEA ≥ 10 ng/ml	0.373	0.766 (0.426–1.377)		
BMI > 24 kg/m^2	0.025	1.936 (1.088–3.447)	0.009	2.206 (1.219–3.993)
Comorbidity	0.963	1.013 (0.577–1.780)		
ASA score 3–4	0.781	1.114 (0.520–2.388)		
Synchronous metastasis	0.173	2.667 (0.650–11.021)		
Primary site colon	0.865	0.953 (0.545–1.665)		
Left hemicolon	0.676	1.200 (0.509–2.830)		
R0 resection	0.001	0.381 (0.216–0.671)	0.007	0.426 (0.230–0.788)
Major liver resection	0.230	1.410 (0.805–2.467)		
Concomitant RFA	0.759	1.110 (0.568–2.170)		
Bilobar distribution	0.006	2.223 (1.256–3.934)	0.039	1.921 (1.032–3.577)
Extrahepatic metastases	0.970	1.017 (0.433–2.388)		
Diameter of metastases ≥ 3 cm	0.247	1.391 (0.796–2.433)		
Solitary metastases	0.061	0.526 (0.269–1.029)		
Operation time ≥ 347min[b]	0.122	1.557 (0.888–2.730)		
Blood loss ≥ 550 ml[b]	0.145	1.740 (0.827–3.661)		
Blood transfusion	0.762	1.109 (0.567–2.171)		
Laparoscopic liver resection	0.742	0.901 (0.485–1.673)		
Postoperative complications	0.027	1.962 (1.081–3.562)	0.017	2.124 (1.143–3.948)
Poorly differentiated	0.640	0.847 (0.424–1.696)		
T3–T4	0.753	1.118 (0.557–2.245)		
Heterochronous resection	0.075	1.664 (0.950–2.912)		
Preoperative chemotherapy				
Oxaliplatin-based regimen	0.474	0.776 (0.387–1.554)		
Cycles > 6	0.077	1.661 (0.947–2.913)		
Targeted therapy	0.773	1.090 (0.606–1.961)		
Second-line chemotherapy	0.186	1.632 (0.789–3.376)		
Neutropenia	0.269	0.722 (0.405–1.287)		
Clinical response	0.232	0.710 (0.405–1.245)		
Pathological response	0.380	0.775 (0.440–1.368)		
Adjuvant chemotherapy	0.013	0.493 (0.281–0.863)	0.006	0.453 (0.256–0.800)

the cancer tissue indicate the impairment of host immune responses and degeneration of tumour tissues, respectively.[31,32] In addition, these anticancer drugs exert their effects dose dependently but not tissue selectively, so these impairment responses occur to a similar extent in both host and cancer tissues. Therefore, it is reasonable that neutropenia reflecting damage to the host immune system correlates with pathological response reflecting damage to the cancer tissues. In the clinic, we can evaluate the efficacy of NAC at the preoperative or early phase of treatment according to whether neutropenia occurs, particularly selecting non-responders, to avoid unnecessary NAC and convert to more intensive neo-adjuvant therapy. Consistent with previous studies, molecular target agents in the preoperative setting and the differentiation of tumours are associated with response rates.[33–35] Interestingly, this study found that preoperative CEA < 10 ng/ml increased favourable response rates. The mechanism of this effect requires further investigation. A combination of these risk factors could likely enhance the prediction accuracy.

Our study revealed that NAC-induced neutropenia was associated with a better PFS but not OS. The reason for the favourable PFS in patients with neutropenia is unknown. Possible mechanisms include the following. Many studies show an association between histological tumour regression in CRLM and better clinical outcomes,[10,36] and similarly, our study shows that favourable pathological response was

associated with a better PFS. In addition, we determined that neutropenia was an independent predictor for favourable pathological response. When patients have a favourable pathological response to NAC, occult metastasis or single tumour cell dissemination (micrometastasis) that would not be removed by resection can be damaged effectively, which is effective in prolonging the PFS. In addition, Okazaki et al.[37] suggested that polymorphic variations of drug metabolic genes were associated with the toxicity of gemcitabine-based therapy. Chemotherapeutic drug metabolism affected the time of drug action in vivo. Therefore, we considered that the relationship of neutropenia and prognosis might be associated with polymorphic variations of drug metabolic genes. On the other hand, a study of advanced gastric cancer patients treated with chemotherapy suggested that the absence of neutropenia might be a sign of an inadequate dose of chemotherapy.[17] We considered that neutropenia might actually be a sign of a sufficient anticancer dose of cytotoxic adjuvant chemotherapy. However, our analysis demonstrated that patients with NAC-induced neutropenia had no significantly better survival than patients without it (mOS 42.3 months vs. 42.5 months, $P = 0.266$). Kim et al.[19] and Sunaga et al.[15] similarly reported that patients receiving chemotherapy with neutropenia did not show advantages in terms of OS, and improvement in PFS was evident in early cervical cancer and colorectal cancer, respectively. The reasons for the equivalent OS between two groups may be as follows: First, our study revealed NAC-induced neutropenia, an independent predictor for favourable pathological response, was associated with a better PFS, but an increased risk of postoperative major complications for patients with severe NAC-induced neutropenia in CRLM and postoperative complications remained significant for a worse OS. The advantage of neutropenia in prolonging survival may be offset by the increased complications. Second, after recurrence, patients received chemotherapy or palliative treatment. It is thought to be possible to obtain prolonged survival by chemotherapy or palliative treatment among patients with recurrence, which impaired the association between OS and PFS as survival outcomes. Third, the OS, defined from the date of surgery to the date of death, as an outcome measure is limited. Interference from non-cancer-related deaths in study may weaken the prognostic influence of cancer biology. In addition, the median follow-up time in this study was 25.2 months, which may be too short to detect significant differences in OS between the two groups.

Recent literature[23,24] correlated high-grade NAC toxicity with higher postoperative morbidity in gastrointestinal carcinomas. This is the first study to support an increased risk of postoperative major complications for patients with NAC-induced severe neutropenia in CRLM. Generally, good tolerance to NAC could inform a healthier and stronger physical condition, and thus less likelihood of developing a complication. In contrast, NAC-induced severe neutropenia is a signal of potentially serious impairment of the host immune response in a patient due to anticancer drugs, which is more likely to develop postoperative major complications. On the other hand, the recent literature reported that sarcopenia was significantly associated with severe chemotherapy toxicity in patients with metastatic colorectal cancer.[38] Sarcopenia was a surrogate biomarker for physical condition and nutritional status.[39] It is widely proven that sarcopenic and frail patients are prone to severe consequences once a complication develops.[40,41] Sarcopenia and frailty were not accounted for in this study, but given the tendency to develop complications due to NAC toxicity, such a condition could be expected.

This study has several inherent limitations that should be acknowledged. First, as with a typical single-institutional and retrospective study, our study is limited by biases. Biases in patient selection and in recording of NAC-induced neutropenia and postoperative complications were hard to eliminate. Some toxicity events and complications, especially less serious ones, could have been underreported. Second, subgroup analysis according to further grading of NAC-induced neutropenia of pathological response and survival was not performed due to the relatively small size of the sample. Third, the KRAS status, an important biomarker for CRLM, was available for only 67.4% of the patients in this study. Despite these limitations, we believe that our study results provide information applicable to routine clinical practice.

In conclusion, the results of the present study suggested an independent predictive role of NAC-induced neutropenia on the occurrence of pathological response, a better PFS and a negative prognostic value of severe neutropenia on postoperative major complications in CRLM patients receiving NAC followed by liver resection. Surgeons should take these factors into consideration throughout the preoperative, intraoperative and postoperative processes. The mechanisms of neutropenia, pathological response, sarcopenia and postoperative complications are interesting topics worthy of further exploration.

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Compliance with Ethical Standards

Conflicts of Interest All authors have no conflicts of interests to disclose.

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Author names in **bold** designate shared co-first authorship

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