Neoadjuvant chemotherapy combined with bevacizumab for resectable colorectal liver metastasis with risk factors for recurrence: a multicenter real-world study

Yizhen Chen*, Yuanyuan Zheng* iD **, Jia Wu*, Rong Ye, Hangdong Jia, Zhenyuan Zhou, Weijie Chen, Linwei Xu, Yuhua Zhang$ and Ming Zheng$** iD

Abstract

Background: Currently, guidelines prohibit the addition of targeted drugs in neoadjuvant chemotherapy (NAC) for initially resectable colorectal liver metastasis (CRLM).

Objective: Nevertheless, efficacy data of NAC combined with bevacizumab (Bev) for initially resectable CRLM with risk factors for recurrence (RFR) are lacking.

Designs: We conducted a multicenter real-world cohort study to retrospectively analyze the efficacy and feasibility of NAC combined with Bev for CRLM with RFR.

Methods: The patients were divided into the NAC alone group and NAC combined with the Bev group. We designated progression-free survival (PFS), objective response rate (ORR), and overall survival (OS) as the outcomes. Kaplan–Meier, Cox proportional hazards regression models, and subgroup analysis were utilized. RFR was a clinical risk score of 3–5. Subgroup analysis was applied to explore which subgroup was more suitable for NAC combined with Bev.

Results: Between 2015 and 2020, this multicenter real-world study encompassed 335 CRLM patients from six medical centers who underwent curative hepatectomy following NAC. Two hundred seventeen patients were in the NAC alone group, and 118 received NAC combined with Bev. The NAC alone group exhibited an ORR of 51.15%, compared to 66.95% in the NAC combined with Bev ($p = 0.005$). The R0 resection rates achieved 91.71% for the NAC alone group and 94.92% for the NAC combined with Bev ($p = 0.276$). Three-year PFS rate was 27.6% for NAC alone and 41.5% for the NAC combined with the Bev group ($p = 0.006$). Furthermore, the 3-year OS was calculated to be 57.0% for the NAC alone and 66.7% for the NAC combined with Bev patients ($p = 0.079$).

Conclusion: For initially resectable CRLM patients with RFR, NAC combined with Bev exhibited a higher ORR and longer PFS.

Chinese clinical trial registry: ChiCTR2400082966.

Keywords: bevacizumab, colorectal cancer, liver metastasis, neoadjuvant chemotherapy, real-world

Correspondence to:
Yuhua Zhang
Department of
Hepatobiliary and
Pancreatic Surgery,
Zhejiang Cancer Hospital,
Hangzhou Institute
of Medicine, Chinese
Academy of Sciences,
Hangzhou, Zhejiang
310022, China
drzhangyuhua@126.com

Ming Zheng
Fujian Key Laboratory
of Geriatrics Diseases,
Department of Geriatric
Medicine, Fujian Provincial
Center for Geriatrics,
Fujian Provincial Hospital,
Fuzhou University
Affiliated Provincial
Hospital, School of
Medicine, Fuzhou
University, Fuzhou, Fujian
350001, China

Shengli Clinical Medical
College of Fujian Medical
University, Fuzhou, Fujian
350001, China
slzm702@126.com

**Yizhen Chen
Yuanyuan Zheng**
Fujian Key Laboratory
of Geriatrics Diseases,
Department of Geriatric
Medicine, Fujian Provincial
Center for Geriatrics,
Fujian Provincial Hospital,
Fuzhou University
Affiliated Provincial
Hospital, School of
Medicine, Fuzhou
University, Fuzhou, Fujian,
China

Shengli Clinical Medical
College of Fujian Medical
University, Fuzhou, Fujian,
China

**Jia Wu
Linwei Xu**
Department of
Hepatobiliary and
Pancreatic Surgery,
Zhejiang Cancer Hospital,
Hangzhou Institute
of Medicine, Chinese
Academy of Sciences,
Hangzhou, Zhejiang, China

Introduction

The 2024 cancer statistics reveal that colorectal cancer (CRC) maintains elevated incidence and mortality rates.[1] During the entire course of CRC, nearly half of the patients will develop liver metastasis.[2,3] Liver metastasis is a major factor affecting the overall prognosis of CRC.[4] The primary objective for colorectal liver metastasis (CRLM) patients is to extend progression-free survival (PFS).[5,6]

Rong Ye
Department of Colorectal Surgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, China

Hangdong Jia
General Surgery, Cancer Center, Department of Hepatobiliary & Pancreatic Surgery and Minimally Invasive Surgery, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China

Zhenyuan Zhou
Anorectal Surgical Department, Hangzhou Red Cross Hospital, Hangzhou, Zhenjiang, China

Weijie Chen
Department of Hepatobiliary Pancreatic Surgery, The First Hospital of PuTian City, Putian, Fujian, China

*These authors share the first authorship.

$These authors share the last authorship.

Currently, curative hepatectomy remains the only approach that can provide the possibility of cure.[7] Despite the benefits of curative hepatectomy, the majority of patients will encounter intrahepatic recurrence or distant metastasis, which substantially diminishes their survival duration.[8,9] CRLM patients with risk factors for recurrence (RFR) (clinical risk score (CRS): 3–5) generally exhibit a worse prognosis.[8] For initially resectable CRLM with RFR, the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) recommend neoadjuvant chemotherapy (NAC).[10,11] However, the use of targeted therapy in NAC for such patients is a matter of considerable debate.[10–14] The 2017 NCCN guidelines specify that the concurrent use of targeted therapy, particularly cetuximab (Cet), is prohibited during NAC for initially resectable CRLM patients.[15] This recommendation is based on the randomized controlled trial published in 2014, which showed that combining NAC with Cet worsened the PFS of initially resectable CRLM patients.[16] For initially resectable CRLM patients with RFR, the role of NAC combined with bevacizumab (Bev) remains unclear.[10,11]

Bev exerts antitumor effects through the inhibition of angiogenesis by binding to vascular endothelial growth factor.[17] The combination therapy with Bev is widely used in initially unresectable CRLM patients, playing a unique role in improving the prognosis of advanced CRLM patients.[18–20] Based on current evidence, we designed a multicenter, real-world retrospective cohort study to explore the efficacy of NAC combined with Bev for resectable CRLM patients with RFR.

Materials and methods

Grouping and study population
Our multicenter, real-world retrospective study analyzed the baseline information and prognostic data of initially resectable CRLM patients with RFR (CRS >2) who were treated from December 2015 to December 2020 at six medical centers: Fujian Provincial Hospital, Zhejiang Cancer Hospital, The First Affiliated Hospital of Fujian Medical University, Zhejiang Provincial People's Hospital, Hangzhou Red Cross Hospital, and The First Hospital of PuTian City. Prior to treatment, initially resectable CRLM patients with

RFR were assessed by the multidisciplinary team (MDT). MDT consists of hepatobiliary surgeons, colorectal surgeons, medical oncologists, and radiologists. These patients underwent NAC and curative hepatectomy. According to the guidelines, MDT at the six included tertiary care centers had nearly uniform inclusion criteria (The procedures and criteria for NAC and surgery were included). The decision to combine treatment with Bev was made in consultation between the MDT and the CRLM patients. In brief, the MDT considered the NAC regimen combined with Bev for CRLM with RFR (CRS >2). In addition, the patient's wishes need to be considered.

All initially resectable CRLM patients with RFR were screened according to the following criteria (Figure 1). Inclusion criteria: (1) Age over 18 years; (2) The primary tumor pathologically confirmed as colorectal adenocarcinoma and had been radically resected (Resection of the primary tumor can be performed simultaneously with hepatectomy or in a two-stage procedure); (3) Liver metastasis pathologically confirmed as CRC liver metastases; (4) Liver metastasis deemed resectable by the MDT prior to NAC; (5) No prior local treatment before NAC, including radiotherapy, and interventional therapy; (6) CRS score >2 points; (7) Intact important organ functions. Exclusion criteria: (1) Preoperative use of any medication that could interfere with trial results (including hormones, immunosuppressants, etc.); (2) History of malignancy other than CRC; (3) Metastases to other parts of the body other than liver; (4) Important clinical data missing, including loss to follow-up; (5) Any disease assessed to affect the trial results. Initially resectable CRLM patients with RFR patients who met the inclusion criteria were categorized into the NAC alone group and the NAC combined with the Bev group, depending on whether Bev was combined. To ensure the integrity of the study, we investigated and appropriately addressed all issues. The ethics committees at all six participating medical centers approved this multicenter, real-world retrospective cohort study. Chinese Clinical Trial Registry: ChiCTR2400082966. The reporting of this study conforms to the STROBE statement[21] (Supplemental Material 1).

Comprehensive treatment procedure
Following admission, initially resectable CRLM patients with RFR underwent individualized
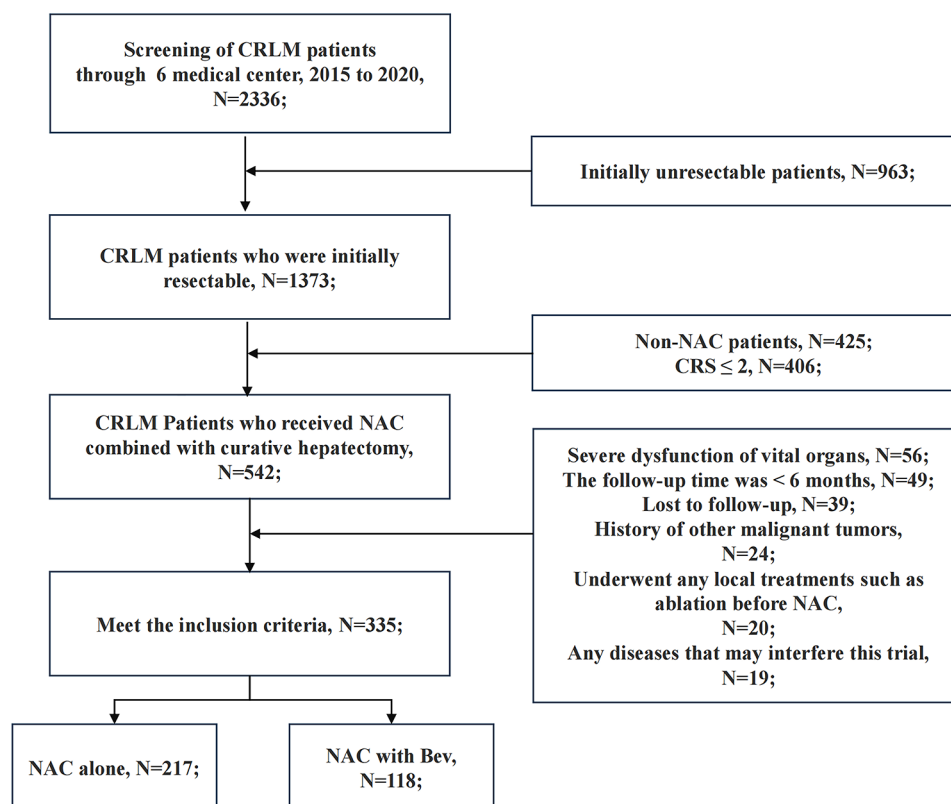
Figure 1. Flow chart of CRLM patients receiving NAC combined with curative hepatectomy.
CRLM, colorectal liver metastasis; CRS, clinical risk score; NAC, neoadjuvant chemotherapy.

treatment after discussion by the MDT. Those who met the inclusion criteria commenced NAC. The choice of regimen was a joint decision made by clinicians and patients. The six medical centers involved in this study employed commonly utilized NAC protocols: CapeOX, mFOLFOX6, and FOLFIRI. Imaging assessments were conducted every two cycles during NAC or whenever the condition of the patient changed (if disease progressed, the next course of treatment was determined by the MDT). Bev was discontinued in the last cycle of NAC to ensure that the final use was at least 5 weeks prior to surgery.[22] Following the last cycle of NAC, imaging was needed, and patients whose liver metastases remained resectable proceeded to surgical treatment. All surgeries were carried out by hepatobiliary surgeons with over 10 years of hepatectomy experience. All liver metastasis, including those responsive to NAC or newly developed tumors, were to be resected. The concurrent use of local treatments such as ablation was not permitted in the treatment plan. Postoperatively, the MDT made decisions

regarding the use of adjuvant chemotherapy based on the specific circumstances.

Definitions
For CRLM, PFS is the alternative endpoint of OS.[5,6] We designated PFS, objective response rate (ORR), and overall survival (OS) as the outcomes. PFS is defined as the time from the date of NAC to the date of disease recurrence, progression, or death.[23] OS is defined as the time from the date of NAC to the date of death or the last follow-up.[23] Complications were defined in accordance with the Clavien–Dindo (CD) classification.[24] The CRS encompasses the following five criteria, with 1 point for each criterion met (3–5 points constituting the high CRS, indicative of high risk of recurrence): nodal positivity of the primary tumor; synchronous liver metastasis or diagnosis of liver metastasis within 12 months of CRC surgery; more than 1 liver metastases; preoperative serum level of carcinoembryonic antigen (CEA) >200 µg/L; and the largest diameter of liver metastasis >5 cm.[10,25] Resectability was

determined by MDT, ensuring that all liver metastasis could be completely resected with an R0 margin and that sufficient functional liver tissue remained.[10,25,26] The MDT assessed the effectiveness of NAC (Using CT and MRI) in accordance with RECIST 1.1 criteria.[27] The group that received only NAC was defined as the NAC alone group, whereas the group that combined NAC with Bev was defined as the NAC combined with Bev group. R0 resection implied the removal of both the CRC and liver metastasis with all detectable tumor masses on imaging and intraoperative exploration being completely resected. General complications included fever, postoperative bleeding, and wound infection.

Follow-up

The six medical centers required patients to undergo disease monitoring every 3 months post-surgery. Tumor markers (CEA, etc.), CT, and endoscopy were collected during the follow-up period. For initially resectable CRLM patients with RFR who showed no tumor progression or distant metastasis within 2 years, the follow-up interval was extended to once every 6 months. For those who remained free of progression or distant metastasis for over 5 years, the follow-up was adjusted to once per year.[23] If any indication of a new tumor was detected during postoperative follow-up examinations, hospitalization for further treatment was necessary. In the event of metastasis or recurrence, the treatment plan needed to be discussed by the MDT, considering options such as surgery, chemotherapy, or local treatment.

Statistical analysis

All data were compiled and subjected to statistical analysis. When continuous variables fulfill the assumptions of normal distribution and variance homogeneity, *Student's t-test* was used to analyze the results (expressed as mean ± standard deviation). Using *continuity correction* or *Pearson's chi-square test* to analyze categorical variables. The 1-year and 3-year PFS and OS were assessed by the Kaplan–Meier survival curves. The relationship of clinical variables with PFS and OS was evaluated using Cox proportional hazards multivariable regression.[23] Further subgroup analysis was conducted to identify which patients would most likely benefit from NAC combined with Bev. The data of this study were analyzed using SPSS (version 26, SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics

From December 2015 to December 2020, 335 initially resectable CRLM patients with RFR were recruited from six medical centers (217 CRLM patients were in the NAC alone group and 118 CRLM patients were in the NAC combined with Bev group). Specifically, the contributions from Fujian Provincial Hospital, Zhejiang Cancer Hospital, The First Affiliated Hospital of Fujian Medical University, Zhejiang Provincial People's Hospital, Hangzhou Red Cross Hospital, and The First Hospital of PuTian City were 118, 41, 88, 39, 33, and 16 cases, respectively. General clinical data of the initially resectable CRLM patients with RFR are available in Table 1. The decision to combine treatment with Bev was made in consultation between the MDT and the CRLM patients. In brief, the MDT considered the NAC regimen combined with Bev for CRLM with RFR (CRS >2). In addition, the patient's wishes need to be considered. In the NAC alone group, there were 106 patients under 60 years (48.85%), while in the combined Bev group, there were 58 patients (49.15%). The baseline characteristics of both groups showed no significant deviation ($p > 0.05$). All patients completed NAC with curative hepatectomy.

Chemotherapy and pathological information

Information related to NAC and postoperative pathology can be found in Table 2. All initially resectable CRLM patients with RFR completed at least two cycles of NAC. The NAC alone group and the NAC combined with the Bev group used an average of 4.46 ± 1.22 and 4.57 ± 1.24 cycles of NAC before surgery, respectively ($p > 0.05$). In the NAC alone group, 72.81% (158/217) of patients used the XELOX regimen, 19.82% (43/217) used the FOLFOX regimen, and 7.37% (16/217) used the FOLFIRI regimen. In the NAC combined with the Bev group, 76.27% (90/118) used XELOX, 18.64% (22/118) used FOLFOX, and 5.08% (6/129) used FOLFIRI ($p > 0.05$). The ORR of NAC combined with the Bev group was 1.31 times that of the NAC alone group (66.95% vs 51.15%, $p = 0.005$). R0 rates achieved by the NAC alone group and the NAC combined with the Bev group were 91.71% (199/217) and 94.92% (112/118), respectively ($p > 0.05$). 84.33% (183/217) of the NAC alone group and 79.66% (94/118) of the NAC combined with the Bev group received postoperative chemotherapy

Table 1. Baseline characteristics of the included CRLM patients.

Variables	NAC alone	NAC combined with Bev	p^a
N	217	118	
Age (years)			
≤60/>60	106/111	58/60	0.958
Gender			
Female/Male	103/114	61/57	0.459
ASA			
I–II/III	118/99	66/52	0.785
Location of primary cancer			
Rectum/Colon	109/108	60/58	0.914
Location of colon cancer			
Left-sided/Right-sided	49/59	25/33	0.779
T stage of primary tumor			
T1–T2/T3–T4	39/178	19/99	0.666
LN metastasis of primary tumor			
N0/N+	28/189	14/104	0.784
Timing of metastasis			
Metachronous/synchronous	64/153	32/86	0.646
CEA at diagnosis, ng/mL			
≤200/>200	99/118	55/63	0.862
Number of liver metastases			
=1/≥2	70/147	36/82	0.742
Largest diameter (cm)			
<5/≥5	73/144	37/81	0.671

[a]Pearson's χ^2 test was used to analyze the basic characteristics.
ASA, American Society of Anesthesiologists; Bev, bevacizumab; CEA, carcinoembryonic antigen; CRLM, colorectal liver metastasis; LN, lymph node; NAC, neoadjuvant chemotherapy.

($p > 0.05$). The NAC alone group and the NAC combined with the Bev group used an average of 4.49 ± 1.30 and 4.33 ± 1.28 cycles of postoperative chemotherapy, respectively ($p > 0.05$).

Perioperative information
Information related to operative details can be found in Table 3. In the NAC alone group, 11.98% (26/217) of patients underwent synchronous CRC curative surgery combined with curative hepatectomy, compared with 10.17% (12/118) in the combined Bev group ($p > 0.05$). No significant variance was observed in terms of operation duration, blood loss during the operation, and length of hospital stay (LOS) between the group receiving NAC alone and the group treated with combined Bev. Postoperative

Table 2. Chemotherapy and pathological outcomes of CRLM patients.

Variables	NAC	NAC combined with Bev	p^a
N	217	118	
NAC regimen			
CapeOX	158	90	0.675
mFOLFOX6	43	22	
FOLFIRI	16	6	
NAC cycles	4.46 ± 1.22	4.57 ± 1.24	0.445
≥3 grade AEs (%)	17.05%	19.49%	0.578
Response to NAC			
CR + PR/SD + PD	111/106	79/39	0.005
Resection status			
R0/R1 + R2	199/18	112/6	0.276
Postoperative chemotherapy			
Yes/No	183/34	94/24	0.280
Postoperative chemotherapy cycles	4.49 ± 1.30	4.33 ± 1.28	0.325

^{a}Pearson's χ^2 test and Student's t-test were used to analyze.
AEs, adverse event; Bev, bevacizumab; CR, complete response; CRLM, colorectal liver metastasis; NAC, neoadjuvant chemotherapy; PD, progressive disease; PR, partial response; SD, stable disease.

complications occurred in 45 patients (20.74%) in the NAC alone group and 21 patients (17.8%) in the NAC combined with Bev. No significant variance was observed between the two groups in liver complications, gastrointestinal complications, respiratory complications, general complications, and major complications (Clavien III–V) ($p > 0.05$). There were no in-hospital or within 30-day postoperative deaths in either group.

Survival analysis

As of January 2024, the median follow-up time of the 335 resectable CRLM patients with RFR was 35.0 (28.0, 44.0) months. The median PFS was 27.0 (17.0, 37.0) months for the NAC alone and 31.0 (21.0, 40.0) months for the NAC combined with Bev. The NAC combined with Bev had a significantly longer PFS than the NAC alone (log-rank; $p = 0.006$) (Figure 2(a)). The 1-year PFS rate was 86.6% for the NAC alone and 93.2% for the NAC combined with Bev ($p = 0.066$). The 3-year PFS were 27.6% for the NAC alone and 41.5% for the
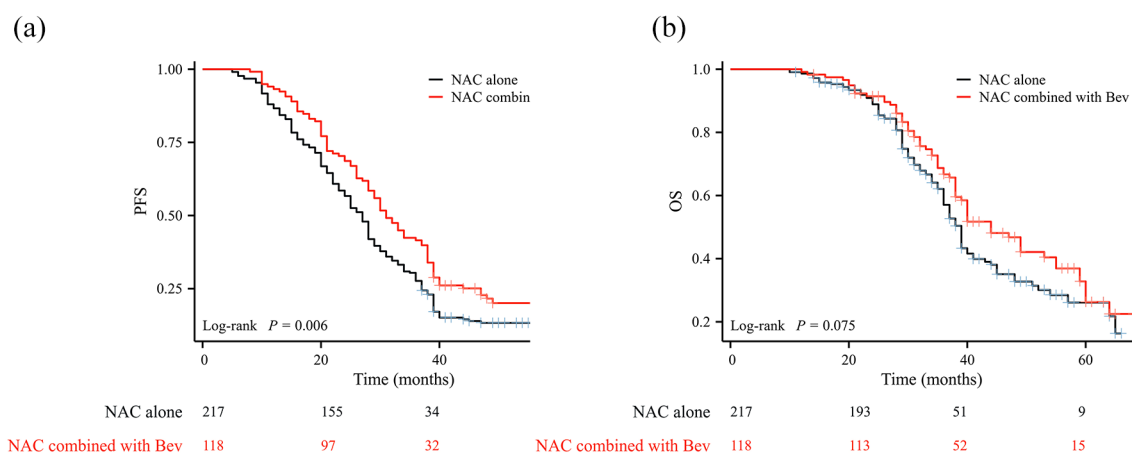
NAC combined with Bev ($p = 0.006$). Cox multivariable regression analysis included factors that whether Bev was combined or not, gender, age, primary tumor location, ASA, T stage, N stage, CEA at diagnosis, timing of metastasis, number of liver metastases, size of largest lesion, response to NAC, resection status, postoperation complications, and postoperative chemotherapy. Cox multivariable regression analysis found that better PFS was independently associated with NAC combined with Bev (hazard ratio (HR) = 1.324; 95% confidence interval (CI): 1.048–1.673; $p = 0.019$) and the higher ORR (HR = 1.299; 95% CI: 1.014–1.663; $p = 0.038$) (Table 4).

The median OS was 33.0 (26.0, 39.0) months for the NAC alone and 38.0 (29.8, 49.0) for the NAC combined with the Bev group. There was no significant difference in OS between the NAC combined with the Bev group and the NAC alone group (log-rank; $p = 0.075$; Figure 2(b)). The 1-year OS was 98.6% for the NAC alone and 99.2% for the NAC combined with Bev

Table 3. Perioperative outcomes of CRLM patients.

Variables	NAC	NAC combined with Bev	p^a
N	217	118	
Simultaneous resection of CRC and liver metastasis; N (%)	26 (11.98)	12 (10.17)	0.617
Operative time (min)	127.90 ± 29.71	123.53 ± 32.31	0.213
Intraoperative blood loss (mL)	240.17 ± 72.26	234.45 ± 72.06	0.489
LOS (days)	4.73 ± 1.12	4.58 ± 1.11	0.222
Postoperative mortality in 30 days; N (%)	0 (0.00)	0 (0.00)	
Postoperative complications; N (%)[b]	45 (20.74)	21 (17.80)	0.518
General complications; N (%)	10 (4.60)	5 (4.24)	0.875
Hepatic complications; N (%)	10 (4.60)	5 (4.24)	0.875
Respiratory complications; N (%)	9 (4.15)	6 (5.08)	0.692
Gastrointestinal complications; N (%)	16 (7.37)	5 (4.24)	0.258
Major complications (Clavien III–V); N (%)	9 (4.15)	3 (2.54)	0.655

[a]Continuity correction, Pearson's χ^2 test, or Student's *t*-test were used to analyze the basic characteristics.
[b]According to the Clavien–Dindo classification.
Bev, bevacizumab; CRC, colorectal cancer; CRLM, colorectal liver metastasis; LOS, length of hospital stay; NAC, neoadjuvant chemotherapy.

Figure 2. Kaplan–Meier survival curve of PFS and OS. (a) PFS, and (b) OS.
OS, overall survival; PFS, progression-free survival.

($p = 1.000$). The 3-year OS was 57.0% for the NAC alone and 66.7% for the NAC combined with Bev ($p = 0.079$). Cox multivariable regression analysis revealed no statistical significance between better OS and NAC combined with Bev ($p = 0.098$; Table 5).

Subgroup analysis

Subgroup analysis was conducted to identify which patients would most likely benefit from NAC combined with Bev. Our forest plot reaffirmed previous results (Figures 3 and 4). In various subgroups, NAC combined with Bev still

Table 4. Analysis of prognostic factors associated with PFS.

Prognostic factor[a]	n	Multivariable	
		HR (95% CI)	p
Group			
NAC combined with Bev	118	1.324 (1.048–1.673)	0.019
NAC alone	217		
Response to NAC			
CR + PR	190		
PD + SD	145	1.299 (1.014–1.663)	0.038

[a]Cox univariate analysis included group (NAC combined with Bev), Gender, Age (years), Primary tumor, ASA, T stage of primary tumor, LN metastasis, CEA at diagnosis (ng/mL), Timing of metastasis, Number of liver metastases, Size of largest lesion (cm), Response to NAC, Resection status, Post-operation complications, and Postoperative chemotherapy. Variables with a significance level of $p < 0.1$ in univariate analysis will be included in the multivariable analysis.
Bev, bevacizumab; CR, complete response; HR, hazard ratio; NAC, neoadjuvant chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 5. Analysis of prognostic factors associated with OS.

Prognostic factor[a]	n	Multivariable	
		HR (95% CI)	p
Group			
NAC combined with Bev	118		
NAC alone	217	1.288 (0.955–1.737)	0.098
ASA			
I–II	184		
III	151	1.254 (0.940–1.674)	0.124
T stage of primary tumor			
T1/T2	58		
T3/T4	277	1.350 (0.900–2.026)	0.147

[a]Cox univariate analysis included group (NAC combined with Bev), Gender, Age (years), Primary tumor, ASA, T stage of primary tumor, LN metastasis, CEA at diagnosis (ng/mL), Timing of metastasis, Number of liver metastases, Size of largest lesion (cm), Response to NAC, Resection status, Post-operation complications, and Postoperative chemotherapy. Variables with a significance level of $p < 0.1$ in univariate analysis will be included in the multivariable analysis.
ASA, American Society of Anesthesiologists; Bev, bevacizumab; HR, hazard ratio; NAC, neoadjuvant chemotherapy; OS, overall survival.

demonstrated superiority over NAC alone in terms of PFS (Figure 3). Interestingly, the advantage of NAC combined with Bev in PFS was particularly pronounced in certain populations, such as those aged ≤60 years, males, primary colon cancer, T stage (I–II), lymph node metastasis from CRC, synchronous liver metastases, a single liver metastasis, and the largest liver metastasis diameter being ≥5 cm. Regarding OS, the benefits of NAC combined with Bev were especially significant in males with primary colon cancer and those with an ASA score of I–II.
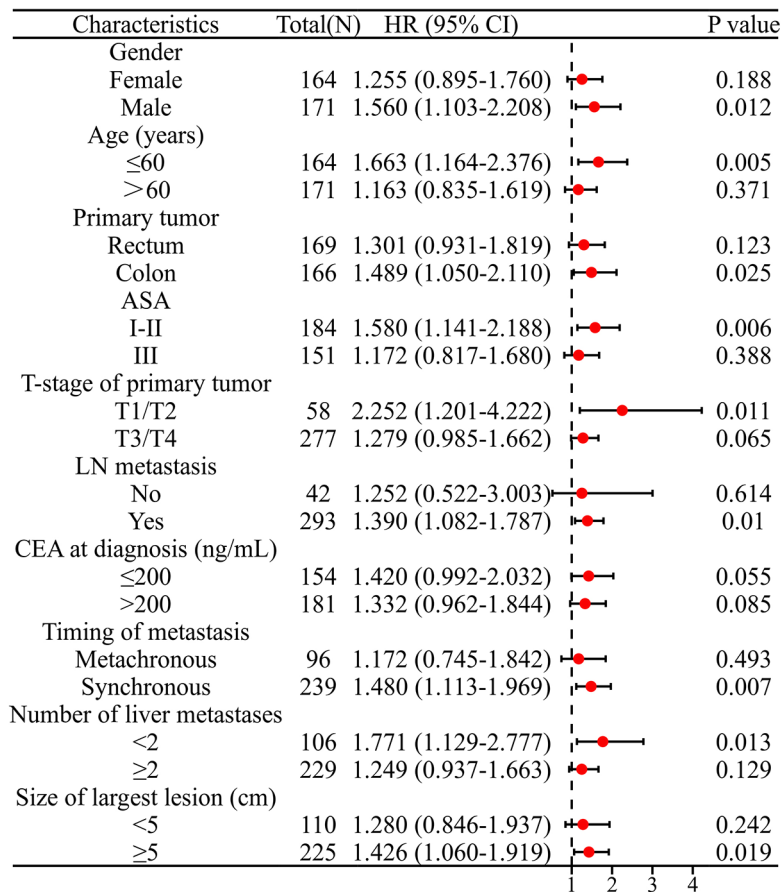
Characteristics	Total(N)	HR (95% CI)	P value
Gender			
Female	164	1.255 (0.895-1.760)	0.188
Male	171	1.560 (1.103-2.208)	0.012
Age (years)			
≤60	164	1.663 (1.164-2.376)	0.005
>60	171	1.163 (0.835-1.619)	0.371
Primary tumor			
Rectum	169	1.301 (0.931-1.819)	0.123
Colon	166	1.489 (1.050-2.110)	0.025
ASA			
I-II	184	1.580 (1.141-2.188)	0.006
III	151	1.172 (0.817-1.680)	0.388
T-stage of primary tumor			
T1/T2	58	2.252 (1.201-4.222)	0.011
T3/T4	277	1.279 (0.985-1.662)	0.065
LN metastasis			
No	42	1.252 (0.522-3.003)	0.614
Yes	293	1.390 (1.082-1.787)	0.01
CEA at diagnosis (ng/mL)			
≤200	154	1.420 (0.992-2.032)	0.055
>200	181	1.332 (0.962-1.844)	0.085
Timing of metastasis			
Metachronous	96	1.172 (0.745-1.842)	0.493
Synchronous	239	1.480 (1.113-1.969)	0.007
Number of liver metastases			
<2	106	1.771 (1.129-2.777)	0.013
≥2	229	1.249 (0.937-1.663)	0.129
Size of largest lesion (cm)			
<5	110	1.280 (0.846-1.937)	0.242
≥5	225	1.426 (1.060-1.919)	0.019

Figure 3. Forest plot evaluating the impact of NAC combined with curative hepatectomy on PFS.
CEA, carcinoembryonic antigen; LN, lymph node; NAC, neoadjuvant chemotherapy; PFS, progression-free survival.

Discussion

This is the first large-sample, multicenter, real-world cohort study comparing the effects of NAC combined with Bev for resectable CRLM patients with RFR. Surprisingly, the comprehensive statistical results of this study revealed that for resectable CRLM patients with RFR, NAC combined with Bev significantly improved PFS and ORR. NAC combined with Bev also exhibited a potential trend toward improvement in OS. As for the concern of increased postoperative complications associated with curative hepatectomy, NAC combined with Bev did not result in an increase. Cox regression and subgroup analysis further validated our findings.

Maximizing the survival span of CRLM patients with RFR stands as a focal point of contemporary research efforts. Administering NAC prior to curative hepatectomy in CRLM patients affords multiple benefits.[28,29] Currently, guidelines including ESMO, NCCN, and the Chinese Society of Clinical Oncology recommend that resectable CRLM patients with RFR (CRS >2) receive NAC prior to curative hepatectomy.[12,15,26,30,31] However, the prognosis for CRLM patients with RFR remains pessimistic. Targeted drugs have become standard in combination therapy for conversion and palliative treatment of CRLM.[12,13,25,26,30–32] Nevertheless, there is controversy regarding the combination of targeted drugs with NAC in resectable CRLM.[12,13,15,25,26] Currently, clinical studies on NAC combined with Bev for resectable CRLM are limited, with only some prospective single-arm trials suggesting a good pathological response.[33,34] The 2017 NCCN guidelines prohibit the addition of targeted therapies during NAC for initially resectable CRLM patients,[15] which has led to few cases of NAC combined with Bev. We increased the sample size by including more medical centers. In addition, considering the cost-effectiveness and ethical issues associated with prospective randomized trials, we
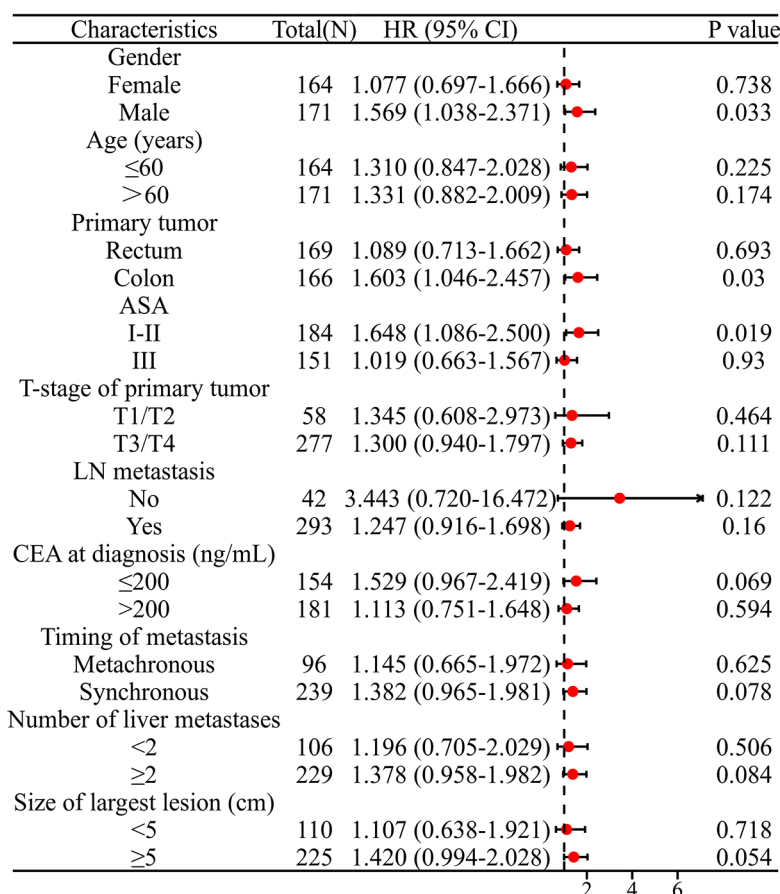
Characteristics	Total(N)	HR (95% CI)		P value
Gender				
Female	164	1.077 (0.697–1.666)		0.738
Male	171	1.569 (1.038–2.371)		0.033
Age (years)				
≤60	164	1.310 (0.847–2.028)		0.225
>60	171	1.331 (0.882–2.009)		0.174
Primary tumor				
Rectum	169	1.089 (0.713–1.662)		0.693
Colon	166	1.603 (1.046–2.457)		0.03
ASA				
I–II	184	1.648 (1.086–2.500)		0.019
III	151	1.019 (0.663–1.567)		0.93
T-stage of primary tumor				
T1/T2	58	1.345 (0.608–2.973)		0.464
T3/T4	277	1.300 (0.940–1.797)		0.111
LN metastasis				
No	42	3.443 (0.720–16.472)		0.122
Yes	293	1.247 (0.916–1.698)		0.16
CEA at diagnosis (ng/mL)				
≤200	154	1.529 (0.967–2.419)		0.069
>200	181	1.113 (0.751–1.648)		0.594
Timing of metastasis				
Metachronous	96	1.145 (0.665–1.972)		0.625
Synchronous	239	1.382 (0.965–1.981)		0.078
Number of liver metastases				
<2	106	1.196 (0.705–2.029)		0.506
≥2	229	1.378 (0.958–1.982)		0.084
Size of largest lesion (cm)				
<5	110	1.107 (0.638–1.921)		0.718
≥5	225	1.420 (0.994–2.028)		0.054

Figure 4. Forest plot evaluating the impact of NAC combined with curative hepatectomy on OS.
CEA, carcinoembryonic antigen; LN, lymph node; NAC, neoadjuvant chemotherapy; OS, overall survival.

designed this multicenter, real-world cohort study to explore this controversial and highly debated topic.[35]

The safety of NAC combined with Bev is fundamental to advancing the application of Bev in resectable CRLM. Surgeons are concerned about the impact of combining Bev on postoperative safety. Adverse events associated with chemotherapy combined with Bev have been previously discussed,[36] which was consistent with our findings. Our research found that NAC combined with Bev did not increase the probability of any postoperative complications. The safety of Bev in post-hepatectomy has been preliminarily confirmed, the result was also validated in a retrospective study in 2014.[37] Compared to NAC alone, no significant difference was observed in the overall complication of NAC combined with Bev ($p = 0.673$).[37] Although not statistically significant, the postoperative complications and LOS in the NAC alone group were slightly higher than in the NAC combined with the Bev group.[37] This finding may be attributed to Bev's capacity to alleviate sinusoidal obstruction syndrome (SOS) induced by oxaliplatin.[38,39] A combination of 18 studies involving 2430 CRLM patients confirmed that chemotherapy regimens combined with Bev reduced the incidence of SOS and postoperative liver failure.[39] However, the specific mechanisms by which Bev reduces SOS need further study. In addition, Bev can cause bleeding and poor healing of liver surgical surfaces.[39] These complications did not occur in our study, and we believe that discontinuing Bev in the last cycle of chemotherapy can essentially avoid the potential for bleeding and poor healing. Bev can be safely given prior to hepatectomy in initially resectable CRLM patients with RFR. This necessitates further validation of the combined regimen on a large-sample scale.

The pathological response of NAC serves as a potent predictor of long-term prognosis after

surgery for CRLM patients.[40,41] The multivariable analysis of 305 CRLM patients who received NAC followed by surgical resection suggested that pathological response ($p = 0.034$) is an independent predictor of survival.[40] Our multivariable analysis also supports the correlation between ORR and better PFS. Pathological response represents a new endpoint of prognostication post-hepatectomy for CRLM. Our study revealed that NAC combined with Bev achieved a higher ORR, which is a result that aligns with our expectations. The first single-arm phase II trial on NAC combined with Bev for resectable CRLM indicated a favorable pathological response (66.7%).[34] A retrospective study in 2014 employing FOLFOX combined with Bev for resectable CRLM patients also achieved an ORR of 66.7%,[37] which aligns with the results of our study. Furthermore, a prospective database analysis of 458 patients who underwent hepatectomy following preoperative chemotherapy indicated that the combination with Bev was independently associated with pathological response.[42] These findings support the use of Bev in resectable CRLM patients with RFR (CRS >2).

For initially resectable CRLM patients with RFR (CRS >2), the ultimate goal of NAC is to improve PFS and OS. The final outcomes of this study are encouraging. NAC combined with Bev compared to NAC alone showed a clear advantage in PFS and a potential OS benefit for initially resectable CRLM patients with RFR. Multivariable and subgroup analyses further confirm the role of NAC combined with Bev in extending PFS in initially resectable CRLM patients with RFR. Although there was no statistical difference in OS, there still appears to be a potential protective effect of combined Bev on OS. There are several possible explanations for better PFS prognostic advantages of NAC combined with Bev in initially resectable CRLM patients with RFR: (1) Combined Bev achieves higher ORR; (2) NAC combined with Bev may better eliminate local and distant micro-metastases, thereby improving PFS; (3) CRLM patients with RFR experience high postoperative relapse rates and poor prognosis. They are more likely to benefit from combined Bev therapy; (4) NAC combined with Bev can reduce complications such as SOS associated with oxaliplatin.[43] Lower postoperative complications are related to better survival prognosis.[44] The 2016 ESMO guidelines consider the combination with Bev in selected patients.[26] The existing study on NAC combined with Bev for the prognosis of initially resectable CRLM is a retrospective study in 2014.[37] A retrospective cohort study included 501 CRLM patients, comparing those who received FOLFOX chemotherapy alone with those combined with Bev, and suggested that NAC combined with Bev did not improve the 3-year OS and PFS.[37] However, in that study, about one-quarter of CRLM patients were initially unresectable.[37] Moreover, there were significant baseline differences between the two groups in that 2014 study.[37] In contrast to that 2014 study, the two groups in our study had balanced baselines, and the target population was initially resectable CRLM patients with RFR. The fact that NAC combined with Bev only showed benefits in terms of PFS, and not a significant increase in OS, might be attributable to the variance in treatment choices after recurrence. This needs to be further validated in future studies.

Personalized treatment is of great significance for initially resectable CRLM with RFR. Subgroup analysis in this study demonstrated that NAC combined with Bev exhibits significant efficacy in specific patients, including those with primary colon cancer, male, synchronous liver metastases, single liver metastases, and tumor diameters >5 cm. These characteristics may be associated with the clinical efficacy of this treatment strategy. Biological differences between colon and rectal cancers influence therapeutic responses, with patients having colon cancer liver metastases more likely to benefit from antiangiogenic therapy, potentially due to their greater dependence on angiogenesis.[45] Gender differences in responses to anticancer therapy have also garnered attention. Some studies suggest that male patients exhibit a more pronounced response to anti-angiogenic therapy than females, possibly related to the regulatory effects of sex hormones on angiogenesis.[46] In addition, CRLM patients with synchronous liver metastases and tumor diameters >5 cm often exhibit greater tumor burden and more rapid metastatic progression, necessitating antiangiogenic therapy to inhibit disease progression. For patients with single liver metastases, the mechanisms underlying the superior efficacy of NAC combined with Bev require further investigation. It is evident that NAC combined with Bev provides promising efficacy in certain CRLM subgroups, and these subgroup characteristics may serve as references for clinical treatment strategy selection. However, further studies are

required to validate the predictive value of these features in guiding CRLM treatment.

These findings have practical clinical significance for initially resectable CRLM patients with RFR. Nonetheless, our study has certain limitations. First, the results are based on a small and specific patient population from six medical centers, which may limit the generalizability of the findings to broader, more diverse populations. Second, the study did not include patients whose tumors progressed to unresectability or those who achieved complete remission without hepatectomy. Lastly, the mutational status (including RAS, RAF, and MMR) is an important target for assessing the prognosis of CRLM patients.[47] Due to the retrospective nature of the study, the KRAS mutation status was not recorded in the cases. These issues need to be addressed by further multicenter, large-sample, and prospective randomized trials.

Conclusion

This large-scale, multicenter, real-world cohort study has yielded promising results. NAC combined with Bev is safe and controllable, providing better pathological remission, and is associated with better PFS. Large-sample prospective studies are needed to further validate the safety and feasibility of NAC combined with Bev for initially resectable CRLM patients with RFR.

Declarations

Ethics approval and consent to participate

This study has been examined by the Institutional Reviewer Board of Fujian Provincial Hospital (K2024-11-027), Zhejiang Cancer Hospital (IRB-2024-1040 (IIT)), The First Affiliated Hospital of Fujian Medical University ([2023] 390), Zhejiang Provincial People's Hospital (ZJPPHEC-2023-204), Hangzhou Red Cross Hospital (2023KY79) and The First Hospital of PuTian City (2024-190). This study has therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Informed consent from these patients was waived by the ethics committee because of the retrospective nature of the study (The Institutional Reviewer Board of Fujian Provincial Hospital, Zhejiang Cancer Hospital, The First Affiliated Hospital of Fujian Medical University, Zhejiang Provincial People's Hospital, Hangzhou Red Cross Hospital, and The First Hospital of PuTian City).

Consent for publication

Not applicable.

Author contributions

Yizhen Chen: Conceptualization; Data curation; Writing – original draft.

Yuanyuan Zheng: Project administration.

Jia Wu: Investigation; Resources; Software; Supervision.

Rong Ye: Formal analysis; Investigation; Validation.

Hangdong Jia: Investigation; Methodology; Supervision.

Zhenyuan Zhou: Formal analysis; Validation.

Weijie Chen: Resources; Supervision.

Linwei Xu: Resources; Software.

Yuhua Zhang: Formal analysis; Supervision; Writing – review & editing.

Ming Zheng: Investigation; Supervision; Writing – review & editing.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data for this study may be requested from the corresponding author where appropriate.

ORCID iDs

Yuanyuan Zheng https://orcid.org/0009-0007-0844-8431

Ming Zheng https://orcid.org/0009-0002-8130-047X

Supplemental material
Supplemental material for this article is available online.

References

1. Siegel RL, Giaquinto AN and Jemal A. Cancer statistics, 2024. *CA Cancer J Clin* 2024; 74: 12–49.

2. McKenzie SP, Vargas HD, Evers BM, et al. Selection criteria for combined resection of synchronous colorectal cancer hepatic metastases: a cautionary note. *Int J Colorectal Dis* 2014; 29: 729–735.

3. Noren A, Eriksson HG and Olsson LI. Selection for surgery and survival of synchronous colorectal liver metastases; a nationwide study. *Eur J Cancer* 2016; 53: 105–114.

4. Zhang C, Dai H and Chen Z. Impact of neoadjuvant chemotherapy on postoperative outcomes for patients with colorectal liver metastases undergoing liver resection. *J Am Coll Surg* 2019; 229: 436.

5. Giessen C, Laubender RP, Ankerst DP, et al. Progression-free survival as a surrogate endpoint for median overall survival in metastatic colorectal cancer: literature-based analysis from 50 randomized first-line trials. *Clin Cancer Res* 2013; 19: 225–235.

6. Ecker BL, Lee J, Saadat LV, et al. Recurrence-free survival versus overall survival as a primary endpoint for studies of resected colorectal liver metastasis: a retrospective study and meta-analysis. *Lancet Oncol* 2022; 23: 1332–1342.

7. Angelsen JH, Horn A, Sorbye H, et al. Population-based study on resection rates and survival in patients with colorectal liver metastasis in Norway. *Br J Surg* 2017; 104: 580–589.

8. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 1996; 77: 1254–1262.

9. Imai K, Allard MA, Benitez CC, et al. Early recurrence after hepatectomy for colorectal liver metastases: what optimal definition and what predictive factors? *Oncologist* 2016; 21: 887–894.

10. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023; 34: 10–32.

11. Kumar D, Neeman E, Zhu S, et al. Revisiting the association of ECOG performance status with clinical outcomes in diverse patients with cancer. *J Natl Compr Canc Netw* 2024; 22: e237111.

12. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2022; 20: 1139–1167.

13. Benson AB, Venook AP, Al-Hawary MM, et al. Colon cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; 19: 329–359.

14. Søreide K. Time to halt perioperative chemotherapy for resectable colorectal liver metastasis? *Br J Surg* 2022; 109: 242–243.

15. Benson AB, Venook AP, Cederquist L, et al. Colon cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; 15: 370–398.

16. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the new EPOC randomised controlled trial. *Lancet Oncol* 2014; 15: 601–611.

17. Vasudev NS and Reynolds AR. Anti-angiogenic therapy for cancer: current progress, unresolved questions and future directions. *Angiogenesis* 2014; 17: 471–494.

18. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; 26: 2013–2019.

19. Gruenberger T, Bridgewater J, Chau I, et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. *Ann Oncol* 2015; 26: 702–708.

20. Yasuno M, Uetake H, Ishiguro M, et al. mFOLFOX6 plus bevacizumab to treat liver-only metastases of colorectal cancer that are unsuitable for upfront resection (TRICC0808): a multicenter phase II trial comprising the final analysis for survival. *Int J Clin Oncol* 2019; 24: 516–525.

21. Okunaka M, Kotani D, Fujiwara H, et al. Prognosis of patients with residual pathological disease after neoadjuvant docetaxel, cisplatin, and 5-fluorouracil therapy and surgery for esophageal squamous cell carcinoma: a retrospective cohort study. *Ther Adv Med Oncol* 2024; 16: 17588359241229432.

22. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 1830–1835.

23. Chen Y, Huang Y, Xu L, et al. Neoadjuvant chemotherapy followed by radiofrequency ablation may be a new treatment modality for colorectal liver metastasis: a propensity score matching comparative study. *Cancers* 2022; 14: 5320.

24. Dindo D, Demartines N and Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240: 205–213.

25. Chinese Society of Clinical Oncology CSCO Diagnosis and Treatment Guidelines for Colorectal Cancer Working Group. Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for colorectal cancer 2018 (English version). *Chin J Cancer Res* 2019; 31: 117–134.

26. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; 27: 1386–1422.

27. Armato SG 3rd and Nowak AK. Revised Modified Response Evaluation Criteria in Solid Tumors for Assessment of Response in Malignant Pleural Mesothelioma (Version 1.1). *J Thorac Oncol* 2018; 13: 1012–1021.

28. Nishioka Y, Shindoh J, Yoshioka R, et al. Clinical impact of preoperative chemotherapy on microscopic cancer spread surrounding colorectal liver metastases. *Ann Surg Oncol* 2017; 24: 2326–2333.

29. Wiseman JT, Guzman-Pruneda F, Xourafas D, et al. Impact of neoadjuvant chemotherapy on the postoperative outcomes of patients undergoing liver resection for colorectal liver metastases: a population-based propensity-matched analysis. *J Am Coll Surg* 2019; 229: 69–77 e62.

30. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol* 2020; 25: 1–42.

31. Yoshino T, Arnold D, Taniguchi H, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. *Ann Oncol* 2018; 29: 44–70.

32. Oki E, Emi Y, Yamanaka T, et al. Randomised phase II trial of mFOLFOX6 plus bevacizumab versus mFOLFOX6 plus cetuximab as first-line treatment for colorectal liver metastasis (ATOM trial). *Br J Cancer* 2019; 121: 222–229.

33. Mukai T, Uehara K, Goto H, et al. Phase II trial of neoadjuvant chemotherapy with S-1 and oxaliplatin plus bevacizumab for colorectal liver metastasis (N-SOG 05 trial). *Jpn J Clin Oncol* 2017; 47: 597–603.

34. Nasti G, Piccirillo MC, Izzo F, et al. Neoadjuvant FOLFIRI+bevacizumab in patients with resectable liver metastases from colorectal cancer: a phase 2 trial. *Br J Cancer* 2013; 108: 1566–1570.

35. Bando H, Ohtsu A and Yoshino T. Therapeutic landscape and future direction of metastatic colorectal cancer. *Nat Rev Gastroentero Hepatol* 2023; 20: 306–322.

36. Bridgewater JA, Pugh SA, Maishman T, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (new EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2020; 21: 398–411.

37. Rong Z, Martel G, Vandenbroucke-Menu F, et al. Impact of peri-operative bevacizumab on survival in patients with resected colorectal liver metastases: an analysis of the LiverMetSurvey. *HPB (Oxford)* 2014; 16: 342–349.

38. Vigano L, Rubbia-Brandt L, De Rosa G, et al. Nodular regenerative hyperplasia in patients undergoing liver resection for colorectal metastases after chemotherapy: risk factors, preoperative assessment and clinical impact. *Ann Surg Oncol* 2015; 22: 4149–4157.

39. Volk AM, Fritzmann J, Reissfelder C, et al. Impact of Bevacizumab on parenchymal damage and functional recovery of the liver in patients with colorectal liver metastases. *BMC Cancer* 2016; 16: 84.

40. Blazer DG, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *J Clin Oncol* 2008; 26: 5344–5351.

41. Xu D, Wang YY, Yan XL, et al. Development of a model to predict pathologic response to chemotherapy in patients with colorectal liver metastases. *J Gastrointest Oncol* 2021; 12: 1498–1508.

42. Maki H, Haddad A, Ayabe RI, et al. TP53 Alteration and its effect on pathologic response are associated with survival after resection of

colorectal liver metastases. *J Gastrointest Surg* 2023; 27: 2597–2600.

43. Overman MJ, Ferrarotto R, Raghav K, et al. The addition of Bevacizumab to Oxaliplatin-based chemotherapy: impact upon hepatic sinusoidal injury and thrombocytopenia. *J Natl Cancer Inst* 2018; 110: 888–894.

44. Artinyan A, Orcutt ST, Anaya DA, et al. Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients. *Ann Surg* 2015; 261: 497–505.

45. O'Dwyer PJ. The present and future of angiogenesis-directed treatments of colorectal cancer. *Oncologist* 2006; 11: 992–998.

46. Zhang X, Cheng L, Gao C, et al. Androgen signaling contributes to sex differences in cancer by inhibiting NF-κB activation in T cells and suppressing antitumor immunity. *Cancer Res* 2023; 83: 906–921.

47. Hsu WH, LaBella KA, Lin Y, et al. Oncogenic KRAS drives lipofibrogenesis to promote angiogenesis and colon cancer progression. *Cancer Discov* 2023; 13: 2652–2673.

Visit Sage journals online
journals.sagepub.com/
home/tam

§ Sage journals