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Contents

Monthly Volume 14 Number 9 September 27, 2022

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

World Journal of Gastrointestinal Surgery

Monthly Volume 14 Number 9 September 27, 2022

Contents

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Contents

ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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ORIGINAL ARTICLE

Retrospective Study

Irinotecan- *vs* oxaliplatin-based regimens for neoadjuvant chemotherapy in colorectal liver metastasis patients: A retrospective study

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Abstract

BACKGROUND

Neoadjuvant chemotherapy (NC) improves the survival outcomes of selected patients with colorectal liver metastasis (CRLM). The benefits of irinotecan-based regimens in these patients are still under debate.

AIM

To compare the benefits of irinotecan- and oxaliplatin-based regimens in patients with resectable CRLM.

METHODS

From September 2003 to August 2020, 554 patients received NC and underwent hepatectomy for CRLM. Based on a 1:1 propensity score matching (PSM) model, 175 patients who received irinotecan were matched to 175 patients who received oxaliplatin to obtain two balanced groups regarding demographic, therapeutic, and prognostic characteristics.

RESULTS

Chemotherapy was based on oxaliplatin in 353 (63.7%) patients and irinotecan in 201 (36.3%). After PSM, the 5-year progression-free survival (PFS) and overall survival (OS) rates with irinotecan were 18.0% and 49.7%, respectively, while the 5-year PFS and OS rates with oxaliplatin were 26.0% and 46.8%, respectively. Intraoperative blood loss, operating time, and postoperative complications dif-

fered significantly between the two groups. In the multivariable analysis, carbohydrate antigen 19-9, RAS mutation, response to NC, tumor size > 5 cm, and tumor number > 1 were inde-pendently associated with PFS.

CONCLUSION

In NC in patients with CRLM, irinotecan is similar to oxaliplatin in survival outcomes, but irinotecan is superior regarding operating time, intraoperative blood loss, and postoperative complications.

Key Words: Colorectal cancer; Liver metastasis; Liver resection; Neoadjuvant chemotherapy

Core Tip: This was the first retrospective cohort study to investigate irinotecan-based regimens for neoadjuvant chemotherapy in patients with colorectal liver metastasis (CRLM) in China. It highlighted the benefits of irinotecan and might contribute to modifying the treatment guidelines for CRLM. Chemotherapy was based on oxaliplatin in 353 (63.7%) patients and irinotecan in 201 (36.3%). After propensity score matching, the 5-year progression-free survival (PFS) and overall survival (OS) rates with irinotecan were 18.0% and 49.7%, respectively, while the 5-year PFS and OS rates with oxaliplatin were 26.0% and 46.8%, respectively.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-related mortality[1]. The liver is the most common site of metastatic involvement, and 25%-30% of CRC patients present with metastatic diseases initially. The long-term survival outcome has been significantly improved by radical resection of the primary tumor and metastases. The overall survival (OS) increased from 36% to 58% at 5 years and 23% to 36% at 10 years, respectively[2,3]. Advances in surgical techniques have improved safety dramatically, resulting in perioperative mortality rates < 5%[4].

Currently, the administration of neoadjuvant chemotherapy (NC) in resectable colorectal liver metastasis (CRLM) patients is increasing as it can increase the radical resection rate and treat occult metastases[5]. 5-Fluorouracil (5-Fu) was previously one of the most common anticancer drugs for CRLM. FOLFIRI (irinotecan, 5-Fu, and leucovorin) and FOLFOX (oxaliplatin, 5-Fu, and leucovorin) regimens have been proven more effective. By combining with antibodies targeting epidermal growth factor receptor and vascular endothelial growth factor, a response rate of about 20% observed in the new era of modern chemotherapy has been greatly increased. Nevertheless, it has been shown that systemic chemotherapy for CRLM might cause injury to the nontumoral liver parenchyma. Sinusoidal obstruction syndrome (SOS) has been identified as being a complication to oxaliplatin-based chemotherapy[6]. Steatohepatitis was considered to be associated with irinotecan-based chemotherapy, especially in obese patients[7]. Because of impaired remnant liver function, chemotherapy-induced liver injury is a major cause of morbidity and mortality after hepatic resection.

For resectable CRLM, oxaliplatin-based regimens have been preferred to irinotecan-based regimens as the first-line treatment because of less alopecia and gastrointestinal toxicity[8]. Irinotecan has been administered to patients with resectable CRLM, but supporting evidence is absent, and whether survival outcomes are improved remains under debated. The present study investigated whether irinotecan might improve progression-free survival (PFS) or OS in patients with resectable CRLM.

MATERIALS AND METHODS

Patient eligibility

This study collected the data from CRLM patients who received NC and underwent hepatic resection between September 2003 and August 2020 at the Hepatopancreatobiliary Surgery Department of Peking

University Cancer Hospital. The demographic and clinical data were retrospectively obtained from a prospective patient database. The inclusion criteria were: (1) Evaluated to be resectable by a multidisciplinary team (MDT) that consisted of surgical oncologists, radiologists, and medical oncologists; (2) Received NC and underwent hepatic resection; (3) No other simultaneous malignancies; (4) 19-80 years of age; and (5) Eastern Cooperative Oncology Group performance status < 2. Patients who underwent only ablation or palliative hepatic resection (R2) were excluded. This study was approved by the Ethics Committee of Beijing Cancer Hospital (No. 2021YJZ06-GZ01), and the requirement for informed consent was waived.

Pretreatment evaluation

All patients were evaluated by physical examination, routine hematology, biochemistry analyses, and measurement of levels of tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (Ca19-9) before treatment. According to standard clinical protocols, computed tomography or magnetic resonance imaging of the abdomen and chest was performed for preoperative staging and evaluation of liver metastasis. In addition, positron emission tomography was performed to rule out any extrahepatic metastasis.

Treatment

The NC regimens consisted mainly of 5-Fu, leucovorin, and oxaliplatin, or 5-Fu, leucovorin, and irinotecan, with or without bevacizumab or cetuximab. There were 353 patients who received a regimen based on oxaliplatin and 201 patients who were treated with a regimen based on irinotecan. Based on World Health Organization criteria, the response to NC was classified according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). MDT discussion assessed the treatment response and the possibility of surgery. If the patient presented with disease progression, a new second-line chemotherapy regimen was recommended.

In surgical treatment, the technical criteria for resectability related to the liver remnant after resection were: (1) Preserving two contiguous segments; (2) Preserving adequate vascular inflow, outflow, and biliary drainage; and (3) Preserving adequate future liver remnant volume (30% in normal liver and 40% in patients with preoperative chemotherapy)[9]. Major hepatic resection was defined to be any resection of three or more segments. All the patients underwent hepatic resection and primary tumor resection. All the specimens were examined for pathological diagnosis after surgery.

Statistical analysis

The continuous variables are expressed using median and range, and the categorical variables are expressed as number (n) and frequency (%). The c^2 or Fisher's exact test was used to compare categorical variables between groups, while the Mann-Whitney U test was afforded to compare the continuous variables between groups. Propensity score matching (PSM) was applied to compensate for the biases between the irinotecan and the oxaliplatin groups in the unmatched cohort with a matching ratio of 1:1 by the nearest neighbor method. The caliper value was set at 0.05. The imbalance before and after PSM was assessed by the standardized mean difference. The following variables were included in the PSM model: Age, sex, primary N stage, number of liver metastases, preoperative CEA/Ca19-9, preoperative clinical risk score (CRS) as proposed by Fong *et al*[10], RAS mutation status, cycles of NC, major hepatic resection, intraoperative radiofrequency ablation combined with hepatic resection, adjuvant chemotherapy, and response to NC. Short-term results were compared between the irinotecan and oxaliplatin groups before and after PSM, such as intraoperative blood loss, intraoperative red blood cell (RBC) transfusion, operating time, and Clavien-Dindo grade of general or surgical complications. PFS was defined as the time from treatment to recurrence, disease progression, or death, whichever occurred first[11]. OS was defined as the interval between hepatic resection and the date of death or last follow-up. Kaplan-Meier survival analysis was performed to compare the PFS and OS before and after PSM using the log-rank test. Uni- and multivariable analyses were conducted with Cox proportional hazards model to identify the independent prognostic factors for PFS after PSM. Significance level was set at 0.05, and SPSS version 23 was used for statistical analyses (IBM, Armonk, NY, United States).

RESULTS

Comparison of irinotecan- and oxaliplatin-treated patients before PSM

We enrolled a total of 554 CRLM patients, with 201 in the irinotecan group and 353 in the oxaliplatin group. Primary N stage, timing of liver metastases, biological agent, staged resection, and operating time were significantly different between the two groups ($P < 0.05$) (Table 1).

Long-term outcomes before PSM

The median follow-up was 41 mo. The intrahepatic and extrahepatic recurrence rates were not significantly different between the irinotecan and oxaliplatin groups. There were no significant

Table 1 Demographic and clinical characteristics of patients before propensity score matching

Patient demographic	All patients (*n* = 554)	Irinotecan group (*n* = 201)	Oxaliplatin group (*n* = 353)	*P* value
Age (yr)	57.1 ± 9.5	56.1 ± 9.6	57.7 ± 9.4	0.056
Sex ration (male:female)	193:361	62:139	131:222	0.137
Primary T stage				0.736
T1-2	64	22	42	
T3-4	490	179	311	
Primary N stage				0.036
N0	191	58	133	
N1-2	363	143	220	
Primary tumor location				0.613
Colon	322	114	208	
Rectum	232	87	145	
Primary tumor side				0.839
Right	75	28	47	
Left	479	173	306	
Timing of liver metastasis				< 0.001
Synchronous	482	157	325	
Metachronous	72	44	28	
Tumor number (median)	3 (1-10)	3 (1-9)	3 (1-10)	0.706
Tumor size (mm, mean ± SD)	27.6 ± 18.2	26.78 ± 17.2	29.0 ± 17.8	0.160
Localization of liver metastases				0.250
Unilobar	226	90	176	
Bilobar	288	111	177	
CEA level (ng/mL)	31.44 ± 85.3	24.93 ± 54.1	35.17 ± 98.65	0.175
CA 19-9 level (IU/mL)	215.4 ± 877.9	194.8 ± 232.8	227.4 ± 185.4	0.847
Extrahepatic metastasis				0.572
No	462	170	292	
Yes	92	31	61	
RAS mutation				0.174
Wildtype	332	128	204	
Mutation	222	73	149	
Biological agent				< 0.001
Cetuximab	118	57	61	
Bevacizumab	187	97	90	
No	249	47	202	
Response				0.209
Complete response	5	0	5	
Partial response	217	81	136	
Stable disease	301	112	189	
Progressive disease	31	8	23	
Cycles	4 (1-16)	4 (1-12)	4 (1-16)	0.430
Concomitant ablation therapy	91	39	52	0.154

CRS				
0-2	274	95	179	
3-5	280	106	174	
Resection				0.002
Simultaneous resection	145	41	104	
Staged resection	409	160	249	
Intraoperative blood loss (mL)	213 ± 198	204 ± 172	218 ± 212	0.437
Intraoperative RBC transfusion	24	10	14	0.289
Intraoperative RBC transfusion (U)	2 (1-12)	2 (1-6)	4 (2-12)	0.026
Operating time (min)	199 ± 74	190 ± 72	204 ± 76	0.039
Hepatic resection				0.357
Major resection	123	49	74	
Minor resection	431	152	279	
Margin status				0.308
Positive	72	30	42	
Negative	482	171	311	
Clavien-Dindo classification				0.057
I-II	164	53	111	
II-V	32	7	25	
Adjuvant chemotherapy				0.153
No	132	41	91	
Yes	422	160	262	

PSM: Propensity score matching; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; RBC: Red blood cell; CRS: Clinical risk score.

differences in 1-, 3-, or 5-year PFS and OS rates ($P > 0.05$; Figures 1A and 1B). In the irinotecan group, the median PFS was 14.0 mo and the 5-year PFS was 25.2%. The median OS was 65 mo and 5-year OS rates was 54.0%. In the oxaliplatin group, the median PFS was 12.5 mo and 5-year PFS was 22.0%. The median OS was 46 mo and 5-year OS was 39.8%.

Comparison of irinotecan- and oxaliplatin-treated patients after PSM

After PSM for the significantly different preoperative and prognostic factors between the two groups, 175 patients from the irinotecan group and 175 from the oxaliplatin group were considered for the matched analyses. When the biases associated with the differences in primary N stage, timing of liver metastases, biological agent, staged resection, intraoperative RBC transfusion, and operating time were removed by PSM, differences in intraoperative blood loss, operating time, and postoperative complications were observed (Table 2).

Long-term outcomes after PSM

The median follow-up was 42 mo. The 1-, 3-, and 5-year OS rates were higher in the irinotecan group than in the oxaliplatin group, while the reverse trend was observed for PFS, but the differences were not significant ($P > 0.05$; Figures 1C and 1D). In the irinotecan group, the 5-year PFS and OS rates were 18.0% and 49.7%, respectively, and the median PFS and OS were 13.5 and 49 mo, respectively. In the oxaliplatin group, the 5-year PFS and OS rates were 26.0% and 46.8%, respectively, and the median PFS and OS were 12.0 and 57 mo, respectively.

Building Cox proportional hazards model

Multivariable Cox regression analysis was performed for the PSM cohort. In the univariate analysis, primary tumor location, synchronous liver metastases, tumor size > 5 cm, tumor number > 1, CRS 3-5, concomitant ablation, bilobar distribution, CA 19-9 > 100 U/mL, RAS mutation, and response rate were associated with PFS ($P < 0.05$) (Table 3). In the multivariate analysis, tumor size > 5 cm, tumor number > 1, RAS mutation, CA 19-9 > 100 U/mL, and response rate to NC were independently associated with PFS ($P < 0.05$).

Table 2 Demographic and clinical characteristics of patients after propensity score matching

Patient demographic	All patients (*n* = 350)	Irinotecan group (*n* = 175)	Oxaliplatin group (*n* = 175)	*P* value
Age (yr)	56.0 ± 4.2	56.2 ± 9.6	55.7 ± 10.1	0.632
Sex ration (male:female)	230:120	121:54	109:66	0.177
Primary T stage				0.433
T1-2	47	21	26	
T3-4	303	154	149	
Primary N stage				0.526
N0	104	51	53	
N1-2	246	125	121	
Primary tumor location				0.756
Colon	205	101	104	
Rectum	145	74	71	
Primary tumor side				0.745
Right	48	25	23	
Left	302	150	152	
Timing of liver metastasis				0.077
Synchronous	283	135	148	
Metachronous	67	40	27	
Tumor number (median)	2 (1-25)	2 (1-25)	2 (1-22)	0.422
Tumor size (mm, mean ± SD)	28.8 ± 18.9	29.2 ± 20.3	28.4 ± 17.5	0.681
Localization of liver metastases				0.493
Unilobar	190	98	92	
Bilobar	160	77	83	
CEA level (ng/mL)	27.81 ± 64.87	24.26 ± 55.81	31.36 ± 72.81	0.307
CA 19-9 level (IU/mL)	228.71 ± 203.76	212.92 ± 145.70	244.51 ± 266.39	0.894
Extrahepatic metastasis				0.311
No	293	150	143	
Yes	57	25	32	
RAS mutation				0.912
Wild type	221	111	110	
Mutation	129	64	65	
Biological agent				0.169
Cetuximab	100	53	47	
Bevacizumab	167	88	79	
No	83	34	49	
Response				0.176
Complete response	1	0	1	
Partial response	144	70	74	
Stable disease	183	98	85	
Progressive disease	22	7	15	
Cycles	4 (0-10)	4 (0-10)	4 (0-10)	0.948
Concomitant ablation therapy	66	36	30	0.464

CRS				0.669
0-2	166	81	85	
3-5	184	94	90	
Simultaneous resection	88	39	49	0.443
Staged resection	262	136	126	
Intraoperative blood loss (mL)	222 ± 211	201 ± 181	264 ± 235	0.024
Intraoperative RBC transfusion	15	8	7	0.117
Intraoperative RBC transfusion (U)	2 (1-12)	2 (1-6)	2 (2-6)	0.281
Operation time (min)	198 ± 73	188 ± 73	208 ± 72	0.012
Hepatic resection				0.886
Major resection	90	42	45	
Minor resection	260	133	130	
Margin status				0.367
Positive	32	17	15	
Negative	318	158	160	
Clavien-Dindo classification				0.019
I-II	102	43	59	
III-V	22	7	15	
Adjuvant chemotherapy				0.352
No	132	41	91	
Yes	422	160	262	

PSM: Propensity score matching; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; RBC: Red blood cell; CRS: Clinical risk score.

DISCUSSION

Compared with 5-Fu alone, irinotecan-based preoperative chemotherapy increased the response rates up to 39%[12], and oxaliplatin improved the response rate from 22% to 51%[13]. With newly developed biological agents, further significant benefits were achieved. Almost 60% of populations were evaluated to have tumor response by combining oxaliplatin-based or irinotecan-based chemotherapy with such targeted agents[14]. In the present study, the 5-year PFS and OS rates were 25.2% and 54.0% for the irinotecan group, respectively. In the oxaliplatin group, the 5-year PFS and OS rates were 22.0% and 39.8%, respectively. Our study was the first retrospective cohort analysis to compare the survival outcomes of irinotecan and oxaliplatin in patients with CRLM.

During the past few years, perioperative chemotherapy for CRLM has been developed remarkably. NC is recommended for resectable CRLM patients to increase the possibility of radical resections. It also might crush the occult metastasis in the liver remnant. Moreover, NC could test whether cancer cells are chemosensitive *in situ*. According to the responses mentioned above, physicians might determine the individualized adjuvant chemotherapy regimen and identify patients who would not benefit from immediate hepatic resection because of tumor progression. Nevertheless, it is still controversial whether NC should be applied for all patients with resectable CRLM. It was reported that a significant improvement in PFS was observed for resectable CRLM patients after NC with FOLFOX4 in the EORTC Intergroup Trial 40983. In contrast, 64% of CRLM patients achieved an objective radiological response after NC, and disease-free survival also improved significantly according to a systematic review of 23 studies comprising 3278 patients. In the present study, tumor size > 5 cm, tumor number > 1, RAS mutation, CA 19-9 > 100 U/mL, and response to NC were independent factors for PFS. This was consistent with previous studies. Hepatic resection is considered a standard treatment for CRLM patients, including special populations, such as those treated with hyperthermic intraperitoneal chemotherapy (HIPEC) and pregnant women[15,16]. HIPEC can be administered before or after surgery, and future studies should examine which HIPEC strategy, and combined with which chemotherapy regimen, would achieve better outcomes.

Oxaliplatin- and/or irinotecan-based NC might cause histological damage, vascular lesions, or steatohepatitis although there are conflicting results in the literature[6,7]. Chemotherapy-induced liver injury could reduce the function of the future remnant liver with an increase in postoperative complications

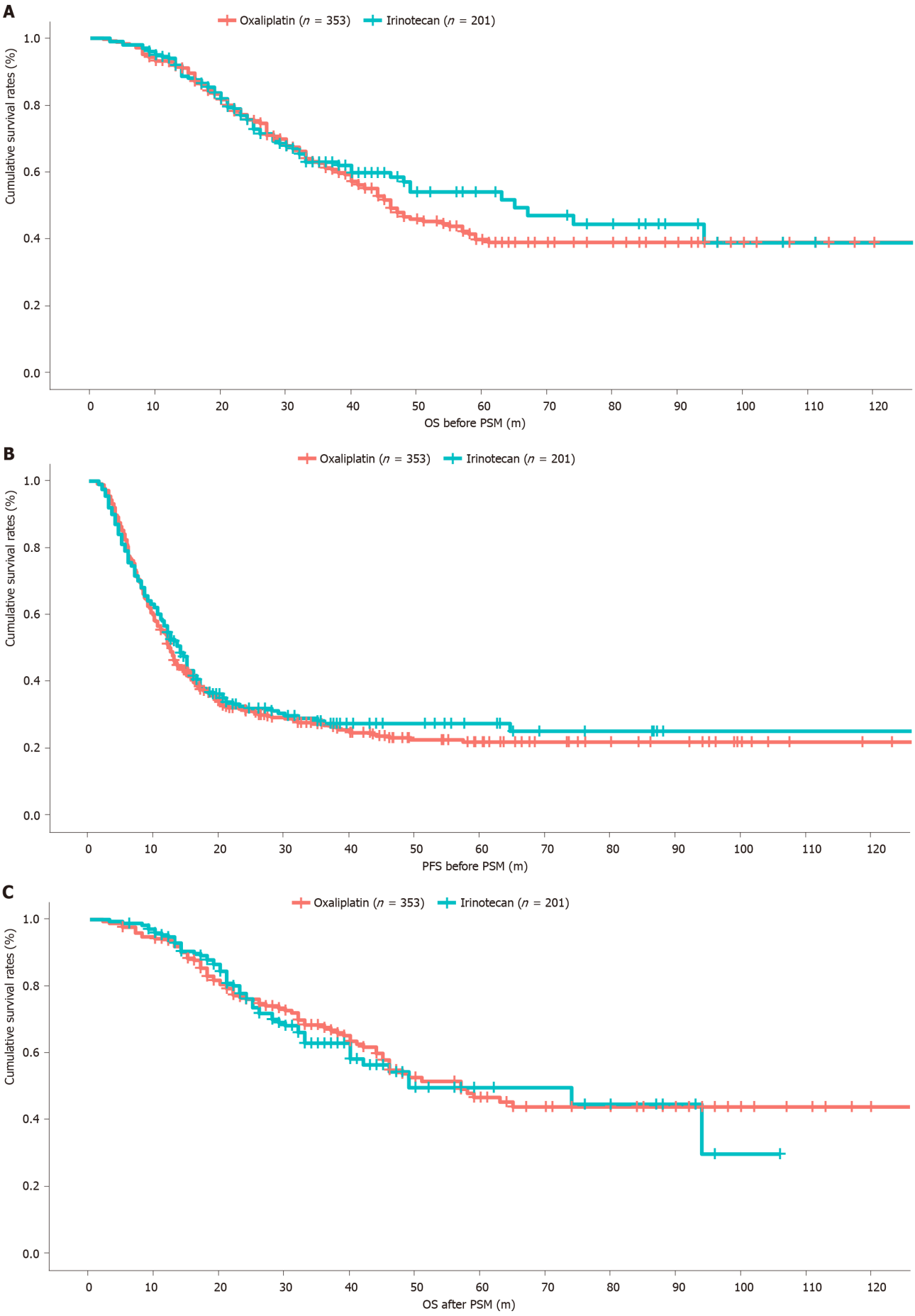
Table 3 Univariable and multivariable analyses of factors associated with progression-free survival

Variable	Univariable analysis			Multivariable analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age, yr						
> 60	Ref					
≤ 60	0.878	0.682-1.131	0.314			
Gender						
Male	Ref					
Female	0.949	0.733-1.230	0.694			
Primary T stage						
1-2	Ref					
3-4	1.183	0.820-1.706	0.369			
Primary N stage						
N0	Ref					
N1-2	1.090	0.952-1.248	0.212			
Location tumor						
Colon	Ref					
Rectum	0.869	0.676-1.116	0.270			
Primary tumor location						
Left	Ref			Ref		
Right	1.508	1.072-2.121	0.018	1.413	0.991-2.015	0.056
Disease-free interval						
> 12 mo	Ref			Ref		
≤ 12 mo	1.487	1.068-2.071	0.019	1.156	0.788-1.696	0.459
CEA						
≤ 200	Ref					
> 200	1.340	0.689-2.607	0.388			
CA 19-9						
≤ 100	Ref			Ref		
> 100	1.528	1.077-2.167	0.017	1.521	1.032-2.241	0.034
Tumor size						
≤ 5 cm	Ref			Ref		
> 5 cm	1.149	1.019-1.554	0.028	1.479	1.062-2.060	0.021
Tumor no.						
≤ 1	Ref			Ref		
> 1	1.702	1.284-2.255	0.000	1.446	1.077-2.146	0.014
CRS						
0-2	Ref			Ref		
3-5	1.665	1.298-2.135	0.000	1.256	0.894-1.765	0.189
RAS status						
Wild	Ref			Ref		
Mutation	1.641	1.276-2.110	0.000	1.468	1.127-1.913	0.004
Extrahepatic metastases						

No	Ref					
Yes	1.081	0.781-1.496	0.638			
Biological agent						
Cetuximab						
Bevacizumab	Ref					
No	1.057	0.910-1.228	0.469			
Response						
Complete response						
Partial response						
Stable disease	Ref			Ref		
Progressive disease	1.564	1.067-2.292	0.022	1.830	1.211-2.764	0.004
Hepatic resection						
Minor	Ref					
Major	0.997	0.753-1.320	0.984			
Concomitant ablation						
No	Ref			Ref		
Yes	1.634	1.195-2.236	0.002	1.002	0.641-1.568	0.992
Stage resection						
No	Ref					
Yes	0.839	0.682-1.033	0.098			
Margin status						
R0	Ref					
R1	0.878	0.581-1.327	0.537			
Distribution						
Unilobar	Ref			Ref		
Bilobar	1.277	1.067-1.528	0.008	1.112	0.875-1.413	0.385
Extrahepatic metastases						
Yes	Ref					
No	1.081	0.781-1.496	0.638			
Adjuvant chemotherapy						
No	Ref					
Yes	0.885	0.654-1.198	0.430			
Clavien-Dino classification						
I-II	Ref					
III-V	1.018	0.833-1.244	0.859			
RBC transfusion						
Yes	Ref					
No	0.857	0.456-1.614	0.634			

PFS: Progression-free survival; HR: Hazard ratio; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; RBC: Red blood cell; CI: Confidence interval; CRS: Clinical risk score.

[17]. Non-parenchymal-sparing strategies have been advocated for radical resection of CRLM and the outcomes associated with these strategies have been reported. Nakano *et al*[17] have reported that major hepatic resection for patients with CRLM with SOS might increase the risk of postoperative complications. Sinusoidal lesions have been associated with an increased blood requirement and higher


A
Oxaliplatin (n = 353)
Irinotecan (n = 201)
Cumulative survival rates (%)
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
80
90
100
110
120
OS before PSM (m)
B
Oxaliplatin (n = 353)
Irinotecan (n = 201)
Cumulative survival rates (%)
PFS before PSM (m)
C
Oxaliplatin (n = 353)
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Cumulative survival rates (%)
OS after PSM (m)

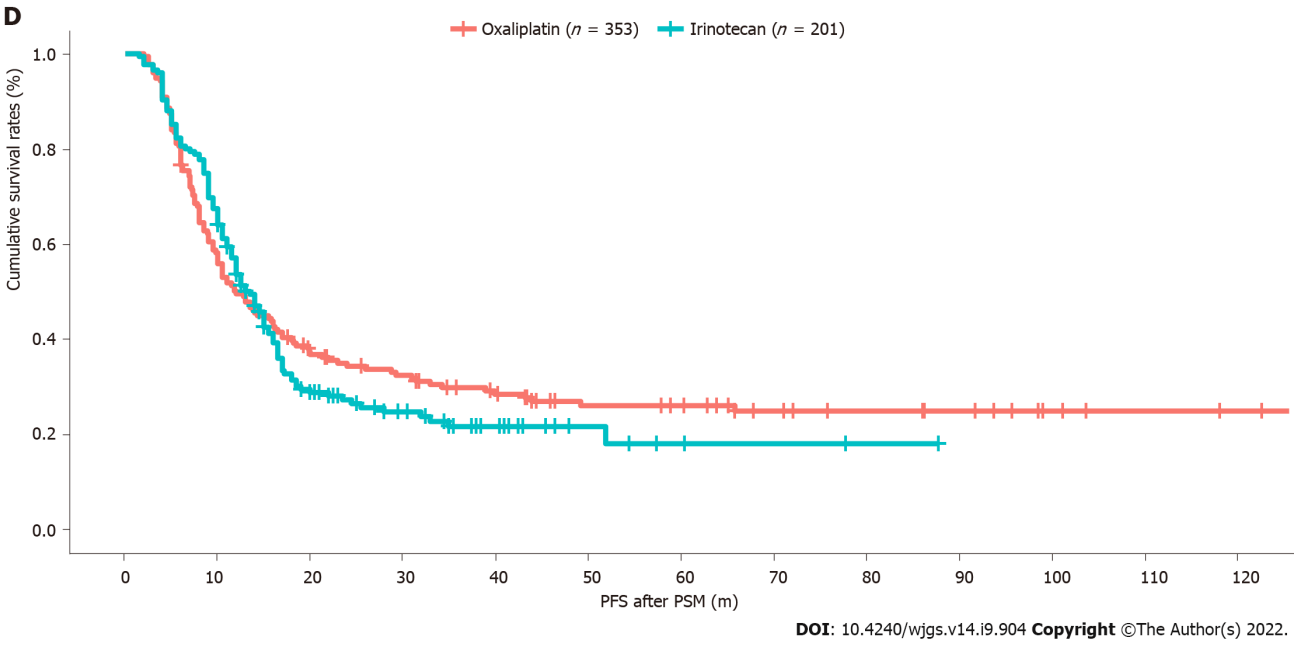

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Figure 1 Overall survival and progression-free survival of patients treated with irinotecan or oxaliplatin before and after propensity score matching. A: Overall survival (OS) of patients treated with irinotecan or oxaliplatin before propensity score matching (PSM) by the Kaplan-Meier method; B: Progression-free survival (PFS) of patients treated with irinotecan or oxaliplatin before PSM by the Kaplan-Meier method; C: OS of patients treated with irinotecan or oxaliplatin after PSM by the Kaplan-Meier method; D: PFS of patients treated with irinotecan or oxaliplatin after PSM by the Kaplan-Meier method. OS: Overall survival; PFS: Progression-free survival; PSM: Propensity score matching.

postoperative liver failure[18,19].

Many studies have attempted to identify predictive factors for chemotherapy-induced liver damage [20]. It is reported that the following could induce SOS: High γ-glutaryl transferase levels, low platelet counts, high aspartate aminotransferase to platelet ratios, and enlarged spleen[21,22]. However, prospective studies are required to confirm the relevance of these factors, and a combination of parameters may provide evidence to establish a diagnosis of SOS preoperatively. Bevacizumab offers an opportunity to prevent SOS and reduces the incidence from 46% to 5% when added to preoperative chemotherapy[23]. It was hypothesized that endothelial cells might secret matrix metalloprotease-9 (MMP-9) and induce SOS in murine models. Bevacizumab might improve SOS by inhibiting vascular endothelial growth factor-dependent induction of MMP-9 and subsequent matrix degradation[24].

The present study had some limitations. First, it was a retrospective cohort study without randomizing for enrolled patients. Second, the included patients were limited after PSM. The sample size should be enlarged in a randomized controlled trial. Third, a validation group would strengthen the present conclusions.

CONCLUSION

In NC for CRLM, irinotecan is similar to oxaliplatin in improving the survival outcomes, but irinotecan is superior in reducing operating time, intraoperative blood loss, and postoperative complications.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) represents an important disease burden worldwide, being the third most common malignancy and the second leading cause of cancer mortality. Many patients are *de novo* metastatic at presentation, and liver metastasis is common in CRC. In selected patients with colorectal liver metastases (CRLM) (*i.e.*, the liver as the only metastatic site), surgery can be performed directly, but some patients with resectable CRLM will require neoadjuvant chemotherapy (NC) to increase the radical resection rate and treat occult metastases. On the other hand, chemotherapy can cause liver injury that will lead to impaired remnant liver function.

Research motivation

For resectable CRLM, oxaliplatin-based regimens have been preferred to irinotecan-based regimens as the first-line treatment because of lower occurrences of alopecia and gastrointestinal toxicity. Irinotecan has been suggested for patients with resectable CRLM, but data for such patients are limited and whether outcomes are improved remains debatable. Therefore, even though NC improves the survival outcomes for selected patients with CRLM, the benefits of irinotecan-based regimens are still under debate.

Research objectives

This study investigated the benefits of irinotecan- *vs* oxaliplatin-based NC regimens in patients with resectable CRLM.

Research methods

At a single hospital in China, 554 patients received NC and underwent hepatectomy for CRLM from September 2003 to August 2020. In order to manage confounding factors, a 1:1 propensity score matching (PSM) was performed. Overall survival (OS), progression-free survival (PFS), intraoperative blood loss, operation time, and postoperative complications were compared between the two groups.

Research results

In the present study, NC regimens were based on oxaliplatin in 353 (63.7%) patients and on irinotecan in 201 (36.3%). Finally, 175 patients who received irinotecan-based NC were matched to 175 who received oxaliplatin-based NC. Hence, the two groups were balanced regarding demographic, therapeutic, and prognostic characteristics. After PSM, the 5-year PFS rates were 18.0% for irinotecan-based NC and 26.0% for oxaliplatin-based NC, while the 5-year OS rates were 49.7% for irinotecan-based NC and 46.8% for oxaliplatin-based NC. Intraoperative blood loss (201 *vs* 264 mL, $P = 0.024$), operation time (188 *vs* 208 min, $P = 0.012$), and postoperative complications (28.6% *vs* 42.3%, $P = 0.019$) all favored the irinotecan-based NC group. In the multivariable analysis, carbohydrate antigen 19-9 [hazard ratio (HR) = 1.52, 95% confidence interval (CI): 1.03-2.24], RAS mutation (HR = 1.47, 95%CI: 1.13-1.91), response to NC (HR = 1.83, 95%CI: 1.21-2.76), tumor size > 5 cm (HR = 1.48, 95%CI: 1.06-2.06), and tumor number > 1 (HR = 1.45, 95%CI: 1.08-2.15) were independently associated with the PFS.

Research conclusions

In patients with CRLM, the PFS and OS are similar between irinotecan- and oxaliplatin-based NC. On the other hand, irinotecan-based NC is superior to oxaliplatin-based NC in terms of shorter operation time, smaller intraoperative blood loss, and fewer postoperative complications.

Research perspectives

This retrospective cohort analysis was the first to compare the OS and PFS of irinotecan-based NC *vs* oxaliplatin-based NC in patients with CRLM. Even though these results can help determine the best options for patients with CRLM, multicenter randomized controlled trials would be required for confirmation. In addition, future studies could examine different dosing strategies in patients with CRLM.

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FOOTNOTES

Author contributions: Liu W designed and performed the research and wrote the paper; Xing BC designed the research and supervised the report; Chen FL designed the research and contributed to the analysis; Wang K, Bao Q, Wang HW, and Jin KM provided clinical advice and reviewed the manuscript; and all authors have read and approved the final version.

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