World Journal of Gastrointestinal Surgery

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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.

INDEXING/ABSTRACTING

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Retrospective Study

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

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

Wei Liu, Feng-Lin Chen, Kun Wang, Quan Bao, Hong-Wei Wang, Ke-Min Jin, Bao-Cai Xing

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Provenance and peer review: Unsolicited article; Externally peer reviewed	Kun Wang, Quan Bao, Hong-Wei Wang, Ke-Min Jin, Bao-Cai Xing, Department of Hepa- topancreatobiliary Surgery, Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University School of Oncology, Beijing Cancer Hospital and Institute, Beijing 100142, China
Peer-review model: Single blind	Corresponding author: Bao-Cai Xing, Department of Hepatopancreatobiliary Surgery, Key

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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-

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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

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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 cancerrelated 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 followup. 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



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Immediation function Print Principate Prino <t< td=""><td>Metachronous</td><td>72</td><td>44</td><td>28</td><td></td></t<>	Metachronous	72	44	28	
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<table-row><table-row><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-row></table-row>	Tumor size (mm, mean ± SD)	27.6 ± 18.2	26.78 ± 17.2	29.0 ± 17.8	0.160
Biolar281177CA lay Can (Marcial)3.44 83.304.94 54.315.15 4.96.300.15 1.00CA 19.9 Lay Can (Marcial)1.94 2.232.24 1.85.400.84.70Cataley Can (Marcial)1.921.001.001.00Cataley Can (Marcial)1.001.001.001.00Cataley Cataley Can (Marcial)<	Localization of liver metastases				0.250
GEA level (ny/ml)J44 ± 85.3J4.93 ± 54.1J5.7 ± 96.4J6.7 ± 97.4CA 19-9 level (U/ml)J5.4 ± 87.9J6.4 ± 22.8J2.7 ± 18.5J6.7 ± 16.7Fix-tarbepatic metastasiTTJ7.2J7.2No46.2J0J2.2J2.2J2.2Na MutationJ2.2J1.2J1.2J1.2Vildype32.0J2.2J2.2J2.2MutationJ2.2J2.2J2.2J2.2No level (agent)J2.2J2.2J2.2J2.2CatximabJ1.8J7.2J2.2J2.2No level (agent)J7.2J2.2J2.2J2.2No level (agent)J1.2J2.2J2.2J2.2CatximabJ1.3J2.2J2.2J2.2J2.2No level (agent)J2.2J2.2J2.2J2.2Catyline (agent)J2.2J2.2J2.2J2.2No level (agent)J2.2J2.2J2.2J2.2No level (agent)J2.2J2.2J2.2J2.2Catyline (agent)J2.2J2.2J2.2J2.2No level (agent)J2.2J2.2J2.2J2.2Catyline (agent)J2.2J2.2J2.2J2.2Catyline (agent)J2.2J2.2J2.2J2.2Catyline (agent)J2.2J2.2J2.2J2.2Catyline (agent)J2.2J2.2J2.2J2.2Catyline (agent)J2.2J2.2J2.2J2.2Catyline (agent)<	Unilobar	226	90	176	
CA 19-9 evel (U/nI)154 87.9194 8 23.827.4 185.40.847Fixmepatienetsass70920.7No4270927Yes9231617Kasmutation1273047Wildype3273047Mutation2273197Chusimab187419701Genziender179707Fevaizamab18497027No1992027Sopose1992027Completersponse512167Stabeldisase01121910Stapesinetineties12121910Stapesineties12812010Stapesineties12121010Stapesineties12121010Stapesineties12121010Stapesineties12121010Stapesineties12121010Stapesineties12121010Stapesineties12121010Stapesineties12121010Stapesineties12121010Stapesineties12121010Stapesineties12121210Stapesineties121212 </td <td>Bilobar</td> <td>288</td> <td>111</td> <td>177</td> <td></td>	Bilobar	288	111	177	
Extrahepatienestissis	CEA level (ng/mL)	31.44 ± 85.3	24.93 ± 54.1	35.17 ± 98.65	0.175
No4627092Yes923161KASmutaion321804Widype3273149Mutaion2273149Celvainab185161Revaziumab1879191No2427302Response1879292Completersponse5002Artial response121310Artial response121312Stabel disease311213Cycles41.018121Cycles111214.01Cycles111111	CA 19-9 level (IU/mL)	215.4 ± 877.9	194.8 ± 232.8	227.4 ± 185.4	0.847
Yea923161RAS nutation52180401Mutation32731901Mutation22731901Glogical agent57611901Cetuxinab183710119No2472011919Resonser500120101Chapteresponse510136101Stabilizaçianda1213101101Stabilizaçianda31123131Stapesponser112101101101	Extrahepatic metastasis				0.572
RAS mutation	No	462	170	292	
Widtype33212894Mutation2207319Biological agent566Cetximab183736Bevacizumab1879703No2437402Rognose2437302Complete response5036Attalianesponse1121819Stabel disease311219Cycles108120Cycles1018120Cycles1018120Cycles101101101	Yes	92	31	61	
Mutaion2207349Biological agent<	RAS mutation				0.174
Biological SystemSecond SystemSecond SystemCeturinab1876Bevacizumab18799No202020Response5020Completersponse503Patial response178116Stable disease31123Progressive disease118120System1212161130System12121212System12121212System12121212System12121212System12121212System12121212System12121212System12121212System12121212System12121212System12121212System13121213System13121313System13131313System13131313System14131313System13131313System14141414System14141414System14141414System1414<	Wildtype	332	128	204	
Cetuximab1185761Bevacizumab1879790No24947202Response50.209Complete response50Partial response1781Stable disease3112Progressive disease11220Question4(16)4(16)	Mutation	222	73	149	
BevaizumabIafo9790No24947202Response500.09Complet response505Partial response2178136Stable disease30112189Progressive disease118121Loge111921Stable disease111010Stable disease101010Stable disease10	Biological agent				< 0.001
No24947202Response	Cetuximab	118	57	61	
Response0.209Completersponse50Partial response2178136Stable disease3011219Progressive disease31823Cycles4(16)4(12)4(16)0.430	Bevacizumab	187	97	90	
Complet response505Partial response217811616Stable disease301121891Progressive disease31823140Cycles4(1-6)4(1-20)4(1-6)0.430	No	249	47	202	
Partial response21781136Stable disease301112189Progressive disease31823Cycles4(1-6)4(1-2)4(1-6)0.430	Response				0.209
Stable disease 301 120 189 Progressive disease 31 8 23 Cycles 4 (1-16) 4 (1-12) 4 (1-16) 0.430	Complete response	5	0	5	
Progressive disease 31 8 23 Cycles 4 (1-16) 4 (1-12) 4 (1-16) 0.430	Partial response	217	81	136	
Cycles 4 (1-16) 4 (1-12) 4 (1-16) 0.430	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	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).



Aliptints (r = 33)Inducan group (r = 17)Oxaliptian group (r = 17)NatureAsyr(r)Sub.14.2Sub.24.96Sub.71.10.10.62Sub.aton (materbank)201.20212.13.40.640.77Privary TaogoTIA0.7T-2.0A12.14.020.2012.14.10.83T-2.1A12.14.112.14.112.14.112.14.1Privary StagoUIIIINoD402512.14.1IINo104.02512.14.1IINo104.012.14.1IIISubary Stago20.40.112.14.1IINo104.021.14.1IIISubary Stago20.14.110.14.1IISubary Stago20.14.120.14.1IISubary Stago20.14.120.14.1II <tr< th=""><th colspan="7">Table 2 Demographic and clinical characteristics of patients after propensity score matching</th></tr<>	Table 2 Demographic and clinical characteristics of patients after propensity score matching						
Anamembra of the series of t	Patient demographic	All patients (n = 350)	Irinotecan group (<i>n</i> = 175)	Oxaliplatin group (<i>n</i> = 175)	P value		
Pinany TangeT244714644T4463161616Pinany Mage10616116Na16121216Na16121216Pinany Manchentain12121616Cadan13131616Cadan1612161616Cadan1612161616Cadan1612161616Cadan1612161616Cadan1612161616Cadan1612161616Cadan1612161616Cadan1612161616Cadan1612161616Cadan1612161616Cadan1612161616Cadan1612161616Cadan1616161616Cadan1616161616Cadan1616161616Cadan1616161616Cadan1616161616Cadan1616161616Cadan1616161616C	Age (yr)	56.0 ± 4.2	56.2 ± 9.6	55.7 ± 10.1	0.632		
T-2Piname </td <td>Sex ration (male:female)</td> <td>230:120</td> <td>121:54</td> <td>109:66</td> <td>0.177</td>	Sex ration (male:female)	230:120	121:54	109:66	0.177		
Flaq93949494Numper State1433Numper State14331Numper State12333State33333State1212333State33333State </td <td>Primary T stage</td> <td></td> <td></td> <td></td> <td>0.433</td>	Primary T stage				0.433		
NameNa1411.Na2412Na2412Colon1312Colon1312Colon1312Retur1313Sigu1313Sigu1313Sigu1313Sigu1313Sigu13Sigu14Sigu13Sigu13Sigu14Sigu14Sigu14Sigu14Sigu14Sigu14Sigu14Sigu14Sigu14Sigu14Sigu14Sigu14 <td< td=""><td>T1-2</td><td>47</td><td>21</td><td>26</td><td></td></td<>	T1-2	47	21	26			
<table-row><table-row><table-row><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-row></table-row></table-row>	T3-4	303	154	149			
N1-2J64J25J26J27J27FinanytamoslacationJ26J18J24J24RedundJ26J2J24J24RightyJ26J2J24J24RightyJ26J2J24J24RightyJ26J24J24J24SyndronovaJ26J24J24J24SyndronovaJ26J24J24J24SyndronovaJ26J24J24J24SyndronovaJ25J24J24J24SyndronovaJ25J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24SyndronovaJ24J24J24J24	Primary N stage				0.526		
IndividuationInformationInformationInformationRefure16161617Refure16161717Refure16161717Refure16161717Refure16161717Syndromo20171817Syndromo17171717Syndromo17171717Syndromo17171717Syndromo17171717Syndromo17171717Syndromo17171717Syndromo17171717Syndromo17171717Syndromo18171718Syndromo18121818Syndromo18121818Syndromo19121218Syndromo19121218Syndromo19121218Syndromo19121318Syndromo19121318Syndromo19121318Syndromo19121318Syndromo19121318Syndromo19121318Syndromo10131414Syndromo10131414 </td <td>N0</td> <td>104</td> <td>51</td> <td>53</td> <td></td>	N0	104	51	53			
Non-Non-Non-Non-Return161616Ringturn161616Right161616Right161616Sindroms161616Sindroms161616Sindroms161616Sindroms202016201620Sindroms20202023202132021Sindroms10212321232021Sindrom10212321243307Sindrom202121243312423307Sindrom212437312423307314Sindrom212437312423307314Sindrom212437312423307314Sindrom212437312423307314Sindrom212437312423307314Sindrom212437312423314314Sindrom212437312423314314Sindrom21243731243314314Sindrom314314314314Sindrom314314314314Sindrom314314314314Sindrom314314314314Sindrom314314314314Sindrom314314314314Sindrom314314314314Sindrom314314314	N1-2	246	125	121			
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Pinary tunor sideRightASSS.LaftJaJaJaJaJa.Tom of the metastas:.SSYendonousASJaJaMachanous.S <td< td=""><td>Colon</td><td>205</td><td>101</td><td>104</td><td></td></td<>	Colon	205	101	104			
<table-row><table-row><table-row><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-row></table-row></table-row>	Rectum	145	74	71			
Left102191102Chringofivernetastast283135484Machonous67407Moronamber(median)21-2321-2324-217Chanoramber(median)28 ± 18.922 ± 2.0324 ± 17.5Chalbart28 ± 18.929 ± 2.0324 ± 17.5Chalbart199824Chalbart107783Chalbart107783Chalbart26 ± 5.813.04 ± 7.25.10.307Chalbart27 ± 20.3721.92 ± 145.7024.51 ± 26.390.394Chalbart29321.92 ± 145.7024.51 ± 26.390.394Chalbart29321.92 ± 145.7024.51 ± 26.390.394Chalbart29.12 ± 0.3721.92 ± 145.7024.51 ± 26.390.394Chalbart29.321.92 ± 145.7024.51 ± 26.390.394No29.321.92 ± 145.7021.92 ± 26.390.394No21.92 ± 26.3921.92 ± 26.3921.92 ± 26.390.394No21.92 ± 26.3921.92 ± 26.3921.92 ± 26.391.31 ± 2	Primary tumor side				0.745		
IningerieventsisJornJornSynchronos8313548Macharonos6700Iunor number (nedian)2125)2123212130.421Tumor size (num mean states)28318.929220.328.417.50.681Catalization cliver metastases107810Tuibolar103781010Catalos (liver metastase)28.12.320.25.313.04.27.810.307Catalos (liver metastase)28.12.35.313.04.27.810.307Catalos (liver metastase)28.12.35.313.04.27.810.301Catalos (liver metastase)28.12.35.313.04.27.810.301Catalos (liver metastase)28.12.35.313.04.27.810.301Catalos (liver metastase)10.31.213.13.27.810.31Na28.12.35.3110.34.27.810.310.31Catalos (liver metastase)10.31.211.310.31Yang (liver metastase)10.311.311.31Yang (liver metastase)10.311.311.31 <td< td=""><td>Right</td><td>48</td><td>25</td><td>23</td><td></td></td<>	Right	48	25	23			
NotSyndroma8313514Medarhomods6707Itomor number (median)(125)21/2321/230.421Tumor size (mm, men ± 50)8.84.8329.2 2.0.38.4 ± 7.50.681Calization of liver metastase109910Tuñobar1083.6 ± 7.50.422Bibbar10778.3 ± 7.2.10.307CAlvel (ng/ml)2.81 ± 4.8.72.42 ± 5.5.13.6 ± 7.2.10.307CAlvel vel (U/ml)2.87 ± 2.0.3.62.2.2 ± 4.5.70.420.42CAlvel vel (U/ml)2.8.1 ± 2.0.3.62.5.2.10.310.31Syntamion2.8.1 ± 2.0.3.61.5.20.310.31Karustain1.5.21.5.20.120.120.12Kutation2.9.1 ± 2.0.3.61.01.01.01.0Mutation2.0.11.11.01.51.6Kutation1.01.31.41.41.41.4Kutation1.01.51.61.61.6Kutation1.01.51.61.61.61.6Kutation1.01.61.61.61.61.6Kutation1.01.61.61.61.61.6Kutation1.01.61.61.61.61.6Kutation1.61.61.61.61.61.6Kutation1.61.61.61.61.6 <t< td=""><td>Left</td><td>302</td><td>150</td><td>152</td><td></td></t<>	Left	302	150	152			
<table-row><table-row><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-row></table-row>	Timing of liver metastasis				0.077		
Inmorpane21-2521-23	Synchronous	283	135	148			
<table-row><table-row><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-row></table-row>	Metachronous	67	40	27			
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Initiobar1909892Bilobar1607783Bibbar6332424370326253132627231CA199 level (U/mL)28.71 ± 20.37621.92 ± 14.57024.51 ± 20.376Brance28.71 ± 20.37621.92 ± 14.57024.51 ± 20.376For29.3015.0014.0011.00Partantoin1961.0011.00Hutaion19.0061.0011.00Bradeatar10.0063.0011.00Bradeatar10.0063.0010.00Caturando10.0063.0010.00Bradeatar10.0053.0061.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0010.00Bradeatar10.0063.0	Tumor size (mm, mean ± SD)	28.8 ± 18.9	29.2 ± 20.3	28.4 ± 17.5	0.681		
Bildear160780CEA levol (ng/ml)28.14 ± 64.8732.64 ± 55.8131.64 ± 72.81CA 10.9 levol (11/ml)28.71 ± 20.36221.92 ± 14.5744.51 ± 26.9.39Fatrahepatic metastasis.31.031.0Farahepatic metastasis.50.014.3.No29.320.020.0Na Canada San (11/ma)20.020.0Yes5757Mutation21.011.010.0Mutation12.0No12.1Mutation10.0	Localization of liver metastases				0.493		
CEA level (ny/mL)2781 ± 64.8724.26 ± 55.8131.66 ± 72.810.307CA 19-9 level (U/mL)208.71 ± 203.7521.92 ± 145.7024.51 ± 26.63.90.894Firshepatie metastasis5531.331.3Ves2935014311Yes572532.319.219.2Ka funtation5510.219.210.2Vid type21111011Matalion1243.26311Fological agent10534711Caturabh107534711No33439111Response106334911Catula feaponse10111Stabe disease183983511Cycls40.01011111Cycls10.01101111Stabe disease13161111Stabe disease1011111Stabe disease1011111Stabe disease101010111Stabe disease1010101011Stabe disease10101010101Stabe disease10101010	Unilobar	190	98	92			
CA19-9 level (U/ml)2871 ± 203761292 ± 1457044.51 ± 266.390.894Fxtrahepatiemetastasis555.115.11No29355.25.25.2Yes5755.25.25.25.2RAS mutation2111105.25.2Wild type2111105.25.2Mutation12645.25.25.2Geograficat Error5.36.25.25.2Cetuximab1005.37.25.25.2No636.27.25.25.2Response10.11.25.25.2Completeresponse144707.45.25.2Stable disease2275.25.25.2Cycles40:0140:016.105.35.2Cycles10.210.21.25.25.2Cycles10.21.21.25.25.2Cycles10.21.21.25.25.2Cycles10.21.21.25.25.2Cycles10.21.21.25.25.2Cycles10.21.21.25.25.2Cycles10.21.21.25.25.2Cycles10.21.21.21.25.2Cycles10.21.21.21.25.2Cycles1.21.2 <td< td=""><td>Bilobar</td><td>160</td><td>77</td><td>83</td><td></td></td<>	Bilobar	160	77	83			
Karahepatic metastasis 574 150 143 Yes 57 25 32 KAS mutation 57 021 011 Mid type 21 111 10 012 Mutation 129 64 63 64 61 64 Biological agent 19 64 63 64 6	CEA level (ng/mL)	27.81 ± 64.87	24.26 ± 55.81	31.36 ± 72.81	0.307		
<table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container>	CA 19-9 level (IU/mL)	228.71 ± 203.76	212.92 ± 145.70	244.51 ± 266.39	0.894		
Yes572532RAS mutation710.912Wild type211110Mutation1296465Biological agent537461Cetuxinab100537974No83349374Response10176Catyle tesponse1407474Stabel disease183888574Progressive disease2275164Queston1001006164Stabel disease6276064	Extrahepatic metastasis				0.311		
RAS mutation	No	293	150	143			
Wild type211110Mutation1296465Biological agent567616Cetuxinab100537074Bevacizumab167887974No8334909174Response1010017Complete response143707474Stabel disease183988574Progressive disease20710048Queston40100401000.988	Yes	57	25	32			
Mutation1996456Biological agent	RAS mutation				0.912		
Biological agent50100Cetuximab1005347Bevacizumab1678890No834090Response5040010Complete response140414Patial response1838880Progressive disease20710Question100100104	Wild type	221	111	110			
Cetuximab1005347Bevacizumab1678899No833499Response50.176Complete response101Partial response1447074Stable disease8839885Progressive disease22715Cycles400040100401000.948	Mutation	129	64	65			
Bevacizumab1678899No833499Response50176Complet response101Patial response1440994Stable disease1839885Progressive disease22715Questo40104010048	Biological agent				0.169		
No833494Response	Cetuximab	100	53	47			
Response0.176Complet response101-Patial response1447074Stable disease1839885Progressive disease22715Questo4010401040100.948	Bevacizumab	167	88	79			
Complete response101-Partial response1447074Stable disease1839885Progressive disease22715Cycles4(0-10)4(0-10)4(0-10)0.948	No	83	34	49			
Partial response1447074Stable disease1839885Progressive disease22715Cycles4(0-10)4(0-10)4(0-10)0.948	Response				0.176		
Stable disease 183 98 85 Progressive disease 22 7 15 Cycles 4 (0-10) 4 (0-10) 0.948	Complete response	1	0	1			
Progressive disease 22 7 15 Cycles 4 (0-10) 4 (0-10) 4 (0-10) 0.948	Partial response	144	70	74			
Cycles 4 (0-10) 4 (0-10) 0.948	Stable disease	183	98	85			
	Progressive disease	22	7	15			
Concomitant ablation therapy 66 36 30 0.464	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						
	Univariable a	nalysis		Multivariable	analysis	
Variable	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						

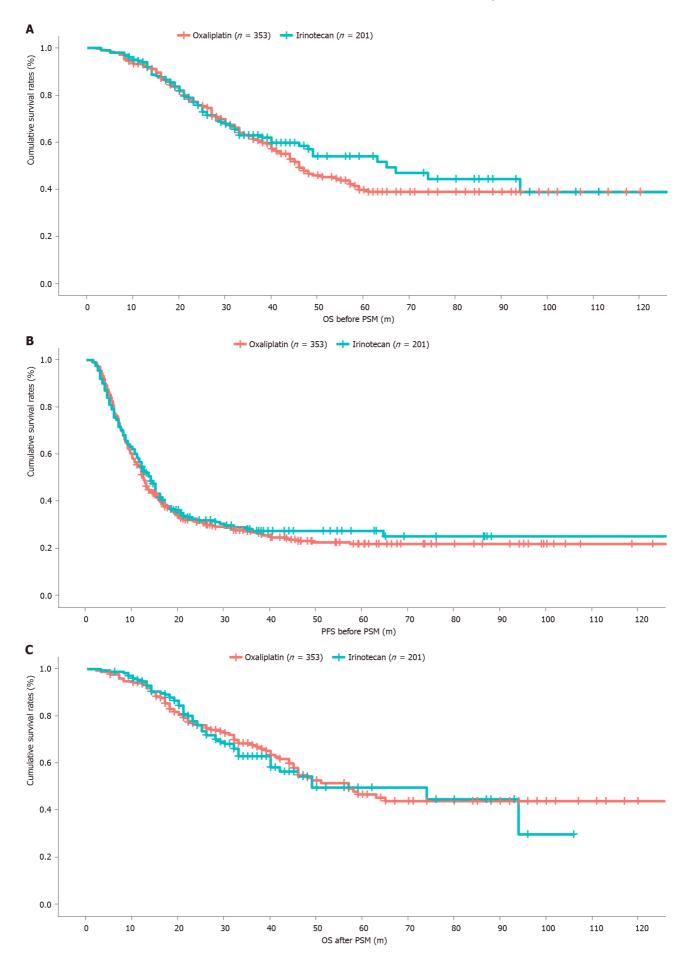
Liu W et al. Neoadjuvant irinotecan in resectable CRLM

NoRefYea10810781-14900.88Biologial agentCatxianalaRefPreadzunaloNa0.901-12280.469ResComplex prosoneStafial AgentoNa0.901-12280.469Complex prosoneStafial AgentoNaNaStafial AgentoNa0.9220.821RefNaProgression closeNaNaStafial AgentoNa0.9220.824RefNaRefConcentiant AllationNa0.931-1230RefNaRefNoNa0.931-12300.841Stafiant StafiantNaNoNa0.931-13200.841Stafiant StafiantNaNaStafiant StafiantNaNaStafiant StafiantNaNaStafiant StafiantNaNaNaStafiantaNaNaNaStafiantaNaNaNaStafiantaNaNaNaStafiantaNaNaNaStafiantaNaNaNaStafiantaNaNaNaStafiantaNaNaNaStafiantaNaNaNaStafiantaNaNaNaStaf							
<table-container>RiskingSet is a set in the set is the se</table-container>	No	Ref					
AdvantionRefRevenue10700.40.12.800.49.0Response	Yes	1.081	0.781-1.496	0.638			
Invariant Provide the service of the service o	Biological agent						
Na1,0570,901.2280,469Reponse	Cetuximab						
ReportComplex personalPatral reportsPatral reportsState and and any personal state of the state of	Bevacizumab	Ref					
ConductorPartial constructorRafRafSpade discaseRafRafPagnessionRafRafPartial constructorRafRafMaranRafRafStandard constructorRafRafConcomitate disconstructorRafRafPartial constructorRafRafStandard constructorRafRafStandard constructorRafRafPartial constructorRafRafPartial constructorRafRafStandard constructorRafRafPartial	No	1.057	0.910-1.228	0.469			
Partial responseImage: Second Sec	Response						
Bable diseaseRefVert of the sectorProgressive disease15400.072-2920.02115300.212-2740.04Haptic resectionKVert of the sectorKKKMori Canaditat ablationNorthown of the sector of the secto	Complete response						
Progressive disease1540.072-2200.0221.801.212-7640.044Hepatic resectionRefAuge <td>Partial response</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Partial response						
IdentifiedIdentifiedMarciRefIdentifiedAnoritatabilitionRefRefNameRefRefSeareactionRefRefNameRefRefSeareactionRefRefNameRefRefSeareactionRefRefSeareactionRefRefNameRefRefSeareactionRefRef <td>Stable disease</td> <td>Ref</td> <td></td> <td></td> <td>Ref</td> <td></td> <td></td>	Stable disease	Ref			Ref		
MinorRefJayica0,531,5200,84ConconitatedationRefNaRefRefStart1,952,2300,020,611,5680,92AgresectionNaNaNaNaNaRefNaNaNaNaNaRefNaNaNaNaNaRefNaNaNaNaNaNaNaNaNaNaNaRefNaNaNaNaNaNaNaNaNaNaNaRefNa<	Progressive disease	1.564	1.067-2.292	0.022	1.830	1.211-2.764	0.004
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And the set of the se	Minor	Ref					
NoRefRefYes1.0341.0320.641.5830.92Sagersection	Major	0.997	0.753-1.320	0.984			
Yes1.641.952.2360.021.020.641.1.580.992Gage resectionRef <td>Concomitant ablation</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Concomitant ablation						
SlagersectionNoRefYes0.8300.682-1.0300.098Margin statusNoSeventoryMargin statusSeventorySeventoryRefSeventorySeventoryDistributionSeventorySeventoryUniobarRefSeventoryBiabar1.2700.0611.120OtaryNo1.1200.875-1.430StatusSeventorySeventoryValueNoNo1.120NoNoNoSeventoryNoSeventorySeventorySeventoryNaSeventorySeventorySeventoryNaSeventorySeventorySeventoryNaSeventorySeventorySeventoryNaSeventorySeventorySeventorySeventorySeventorySeventorySeventorySeventorySeventorySeventorySeventoryNaSeventorySeventor	No	Ref			Ref		
NoRefYes0.8300.821.0300.98Harjin status	Yes	1.634	1.195-2.236	0.002	1.002	0.641-1.568	0.992
Yes0.8390.682-1.0330.98Marjin statusKarKarRoRafKarRa0.8700.571.427DistributionKarKarUniobarRafKarBiabar1.0200.671.528Biabar1.1200.875.4130.385KarmentastasesKarKarKarYesRafKarKarKarNo0.8100.781.4960.638KarAdjournt chemotherapyKarKarKarNa0.851.0320.430KarInfoRafKarKar <trr>Info</trr>	Stage resection						
Magin statusR0R6R10.8780.511.327Distribution5.311.3270.531.327DistributionKKChildbarR6KBiolar1.0270.081Biobar1.2700.071.5280.081DistributionsKKChildbarR6KStatusKKPageR6KNo0.810.81.496Alguant chemotyKKPageR6KStatusSastatAlguant chemotyKKPageR6KStatusSastatAlguant chemotyKKPageR6KStatusSastatSastatPageR6KStatusSastatSastatPageR6KStatusSastatSastatPageR6KStatusSastatStatusSastatSastatPageR6KStatusSastatSastatStatusSastatSastatStatusSastatSastatStatusSastatSastatStatusSastatSastatStatusSastatSastatStatusSastatSastatStatusSastatSastatStatusSastatSastatStatusSastatSastatStatusSastatSastatStatus <td>No</td> <td>Ref</td> <td></td> <td></td> <td></td> <td></td> <td></td>	No	Ref					
R0RíR1087087DistibutionUniobarRáInibar1270.071.528Bidoar1.120.875.413Bidoar1.270.081AtrapationetastasesYaRáNo1.81Agount chemotherapyNa0.811.493Aguard chemotherapyYaRáSa0.651.198Aguard chemotherapyPiaAfaAguard chemotherapyInfo0.851Aguard chemotherapyPia0.863Aguard chemotherapyPia0.81Aguard chemotherapyPia0.81Aguard chemotherapyPia0.81Aguard chemotherapyPia0.81Aguard chemotherapyPia0.81Aguard chemotherapyPia0.81Aguard chemotherapyPia0.81Aguard chemotherapyPia0.81Aguard chemotherapyPia0.81Pia0.81Pia0.81Pia0.81Pia0.81Pia0.81Pia0.81Pia0.81Pia0.81Pia0.81Pia0.81Pia0.81Pia0.81Pia0.81Pia0.81 <trr>Pia0.81<trr>Pia0.81<td>Yes</td><td>0.839</td><td>0.682-1.033</td><td>0.098</td><td></td><td></td><td></td></trr></trr>	Yes	0.839	0.682-1.033	0.098			
R10.8780.581.3270.537DistributionUniobarRefBidoar1.2701.067.1.5280.0811.1200.875.1.430.855Extanepationetastases </td <td>Margin status</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Margin status						
DistributionRefGlobar2.7700.067.12800.11200.875.14300.85Bidbar1.1200.875.14300.850.850.85CatrahepatienetastasesNo0.810.81.49600.638Adjuvant chemotherapyNoRefPage0.8500.654.19800.430Page0.8510.654.19800.430 </td <td>R0</td> <td>Ref</td> <td></td> <td></td> <td></td> <td></td> <td></td>	R0	Ref					
Initial ReformanceRefBiologn1.2701.071.5280.0801.1200.875.1.4300.851BiolognServiceServiceServiceServiceServiceServiceServiceNo1.8100.781.1.4900.632ServiceServiceServiceServiceServiceServiceAdjuant chemotherapyService </td <td>R1</td> <td>0.878</td> <td>0.581-1.327</td> <td>0.537</td> <td></td> <td></td> <td></td>	R1	0.878	0.581-1.327	0.537			
Biolar1.271.067.1.520.081.1120.875.1.430.385Extrahepatie metastasesFFF<	Distribution						
Extrahepatic metastasesYesRefNo1.080.781-1.496Adjuvant chemotherapy-YesRefYes0.8500.654-1.198Clavien-Dino classification-FIRefInfvNameAnge0.833-1.248Kesteransfusion-YesRefYes	Unilobar	Ref			Ref		
YesRefNo1080.781.4960.638Adjuvart chemotherapyNoRef-Yes0.8500.654.1980.430Clavien-Diro classificationFIRef-InV0.1800.831.2440.859RefYesRef-Human MarkRefStoransfusionYesRef-YesRef-YesNet- <td>Bilobar</td> <td>1.277</td> <td>1.067-1.528</td> <td>0.008</td> <td>1.112</td> <td>0.875-1.413</td> <td>0.385</td>	Bilobar	1.277	1.067-1.528	0.008	1.112	0.875-1.413	0.385
No1.0810.781-1.4960.638Adjuvant chemotherapyNoRefYes0.8500.654.1.980.430Clavien-Dino classificationFIIRefInV0.8130.833-1.2440.859RefYesRefYesRefYesRef	Extrahepatic metastases						
Adjuvant chemotherapyNoRefYes0.8500.654.1980.430Clavien-Dino classificationYesYesI-IQRefYesNessInVo1.0180.833.12440.859RefYesRefYes	Yes	Ref					
NoRefYes0.8500.654.1980.430Clavien-Dino classificationI-IIRefIII-V1.0180.833.12440.859RBC transfusionYesRef	No	1.081	0.781-1.496	0.638			
Yes0.8850.654-1.1980.430Clavien-Dino classificationI-IIRefIII-V1.0180.833-1.244RBC transfusionYesRef	Adjuvant chemotherapy						
Clavien-Dino classificationI-IIRefIII-V1.0180.833-1.2440.859RBC transfusionVVYesRefV	No	Ref					
I-IIRefIII-V1.0180.833-1.2440.859RBC transfusion	Yes	0.885	0.654-1.198	0.430			
III-V 1.018 0.833-1.244 0.859 RBC transfusion	Clavien-Dino classification						
RBC transfusion Yes Ref	I-II	Ref					
Yes Ref	III-V	1.018	0.833-1.244	0.859			
	RBC transfusion						
No 0.857 0.456-1.614 0.634	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





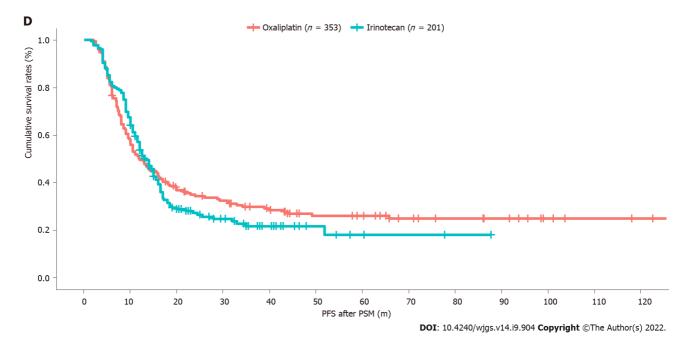


Figure 1 Overall survival and progression-free survival of patients treated with irinotecan or oxaliplatin before and after propensity score matching. A: Overall survival (OS) of patients treated with irinotecan or oxaliplatin before propensity score matching (PSM) by the Kaplan-Meier method; B: Progression-free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

- Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 1 **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]
- Adam R, Kitano Y. Multidisciplinary approach of liver metastases from colorectal cancer. Ann Gastroenterol Surg 2019; 2 3: 50-56 [PMID: 30697610 DOI: 10.1002/ags3.12227]
- Leung U, Gönen M, Allen PJ, Kingham TP, DeMatteo RP, Jarnagin WR, D'Angelica MI. Colorectal Cancer Liver 3 Metastases and Concurrent Extrahepatic Disease Treated With Resection. Ann Surg 2017; 265: 158-165 [PMID: 28009741 DOI: 10.1097/SLA.000000000001624]
- Breitenstein S, DeOliveira ML, Raptis DA, Slankamenac K, Kambakamba P, Nerl J, Clavien PA. Novel and simple preoperative score predicting complications after liver resection in noncirrhotic patients. Ann Surg 2010; 252: 726-734 [PMID: 21037427 DOI: 10.1097/SLA.0b013e3181fb8c1a]
- Liu W, Zhang W, Xu Y, Li YH, Xing BC. A Prognostic Scoring System to Predict Survival Outcome of Resectable Colorectal Liver Metastases in this Modern Era. Ann Surg Oncol 2021; 28: 7709-7718 [PMID: 34023948 DOI: 10.1245/s10434-021-10143-6
- Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, Dousset B, Morel P, Soubrane O, Chaussade S, Mentha G, Terris B. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004; 15: 460-466 [PMID: 14998849 DOI: 10.1093/annonc/mdh095]
- Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, Eng C, Lauwers GY, Mino-Kenudson M, Risio M, Muratore A, Capussotti L, Curley SA, Abdalla EK. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006; 24: 2065-2072 [PMID: 16648507 DOI: 10.1200/JCO.2005.05.3074]
- Samura H, Oki E, Okumura H, Yoshida T, Kai S, Kobayashi K, Kinjo T, Mori S, Tohyama T, Ohgaki K, Kawanaka H, 8 Makiyama A, Ureshino N, Kotaka M, Shimose T, Ando K, Saeki H, Baba H, Maehara Y, Mori M. A phase I/II study of S-1 and irinotecan (IRIS) combined with cetuximab in patients with RAS wild-type metastatic colorectal cancer (KSCC1401). Cancer Chemother Pharmacol 2020; 86: 285-294 [PMID: 32734398 DOI: 10.1007/s00280-020-04108-x]
- 9 Adams RB, Aloia TA, Loyer E, Pawlik TM, Taouli B, Vauthey JN; Americas Hepato-Pancreato-Biliary Association; Society of Surgical Oncology; Society for Surgery of the Alimentary Tract. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. HPB (Oxford) 2013; 15: 91-103 [PMID: 23297719 DOI: 10.1111/j.1477-2574.2012.00557.x
- 10 Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999; 230: 309-18; discussion 318 [PMID: 10493478 DOI: 10.1097/00000658-199909000-00004]
- Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-11 Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, Gruenberger T; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013; 14: 1208-1215 [PMID: 24120480 DOI: 10.1016/S1470-2045(13)70447-9]
- 12 Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M,



Gruia G, Awad L, Rougier P. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000; 355: 1041-1047 [PMID: 10744089 DOI: 10.1016/s0140-6736(00)02034-1

- 13 de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000; 18: 2938-2947 [PMID: 10944126 DOI: 10.1200/JCO.2000.18.16.2938]
- Behrenbruch C, Prabhakaran S, Udayasiri D, Hollande F, Michael M, Hayes I, Heriot A, Knowles B, Thomson B. 14 Survival benefit of neoadjuvant chemotherapy and surgery versus surgery first for resectable colorectal liver metastases: a cohort study. ANZ J Surg 2021; 91: 1196-1202 [PMID: 33543551 DOI: 10.1111/ans.16613]
- 15 Bacalbasa N, Balescu I, Cretoiu D, Halmaciu I, Dimitriu M, Socea B, Diaconu C, Iliescu L, Savu C, Filipescu A, Stoica C, Stiru O. Determination of whether HIPEC is beneficial in patients with synchronous peritoneal and liver metastases from colorectal cancer (Review). Exp Ther Med 2021; 22: 1267 [PMID: 34594404 DOI: 10.3892/etm.2021.10702]
- Predescu D, Boeriu M, Constantin A, Socea B, Costea D, Constantinoiu S. Pregnancy and Colorectal Cancer, from 16 Diagnosis to Therapeutical Management - Short Review. Chirurgia (Bucur) 2020; 115: 563-578 [PMID: 33138893 DOI: 10.21614/chirurgia.115.5.563]
- Nakano H, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P, Bachellier P, Jaeck D. Sinusoidal injury 17 increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg 2008; 247: 118-124 [PMID: 18156931 DOI: 10.1097/SLA.0b013e31815774de]
- Pathak S, Tang JM, Terlizzo M, Poston GJ, Malik HZ. Hepatic steatosis, body mass index and long term outcome in 18 patients undergoing hepatectomy for colorectal liver metastases. Eur J Surg Oncol 2010; 36: 52-57 [PMID: 19879103 DOI: 10.1016/j.ejso.2009.09.004]
- 19 Wicherts DA, de Haas RJ, Sebagh M, Ciacio O, Lévi F, Paule B, Giacchetti S, Guettier C, Azoulay D, Castaing D, Adam R. Regenerative nodular hyperplasia of the liver related to chemotherapy: impact on outcome of liver surgery for colorectal metastases. Ann Surg Oncol 2011; 18: 659-669 [PMID: 20976564 DOI: 10.1245/s10434-010-1385-5]
- 20 Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 2007; 94: 274-286 [PMID: 17315288 DOI: 10.1002/bjs.5719]
- Soubrane O, Brouquet A, Zalinski S, Terris B, Brézault C, Mallet V, Goldwasser F, Scatton O. Predicting high grade 21 lesions of sinusoidal obstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. Ann Surg 2010; 251: 454-460 [PMID: 20160638 DOI: 10.1097/SLA.0b013e3181c79403]
- Overman MJ, Maru DM, Charnsangavej C, Loyer EM, Wang H, Pathak P, Eng C, Hoff PM, Vauthey JN, Wolff RA, 22 Kopetz S. Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. J Clin Oncol 2010; 28: 2549-2555 [PMID: 20406923 DOI: 10.1200/JCO.2009.27.5701]
- Rubbia-Brandt L, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, Brezault C, Soubrane O, Abdalla EK, Vauthey 23 JN, Mentha G, Terris B. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatinassociated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology 2010; 56: 430-439 [PMID: 20459550 DOI: 10.1111/j.1365-2559.2010.03511.x]
- Deleve LD, Wang X, Tsai J, Kanel G, Strasberg S, Tokes ZA. Sinusoidal obstruction syndrome (veno-occlusive disease) in the rat is prevented by matrix metalloproteinase inhibition. Gastroenterology 2003; 125: 882-890 [PMID: 12949732 DOI: 10.1016/s0016-5085(03)01056-4]





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