RESEARCH ARTICLE

Editorial Process: Submission:02/22/2023 Acceptance:09/17/2023

Predictive Factors for the Survival Outcomes of Preoperative Chemotherapy in Patients with Resectable and Borderline Resectable Colorectal Cancer with Liver Metastasis

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Abstract

Background: Preoperative chemotherapy increases resectability in borderline resectable colorectal liver metastasis (CRLM) patients who undergo curative liver surgery. Most clinical risk scores and other predictive factors for survival have been extensively studied in patients who undergo upfront liver surgery. However, predictive factors of CRLM patients who received preoperative chemotherapy remains controversial. **Methods:** CRLM patients who received preoperative systemic therapy followed by curative liver surgery at our institution between 1/2012 and 12/2018 were included. This study aimed to investigate factors that predicted the outcomes of preoperative systemic treatment, optimal dose/duration, and toxicity in patients with CRLM. **Outcomes:** Ninety-eight patients were eligible for analysis. Most patients received oxaliplatin-based chemotherapy (72.7%), while 15.9% received both oxaliplatin and irinotecan. Biologic agents were administered in 48.9% of patients. Overall, chemotherapy-induced liver injury was observed in 38.5%. The median disease-free survival (DFS) and overall survival (OS) were 8.7 months and 3.6 years, respectively. Baseline, pre-surgery, and increased Fong scores after preoperative chemotherapy were significantly associated with DFS and OS. In multivariate analysis, a high Fong score at baseline (p=0.018) was significantly associated with shorter DFS, whereas male sex (p=0.040) and liver surgery (p=0.044) were related to longer OS. **Conclusion:** In our study, Fong clinical risk scores, female sex, and liver surgery as a part of liver-directed therapy were independent prognostic factors for survival in CRLM patients who received preoperative chemotherapy. These clinical factors should be considered as an option to guide physicians' decisions in selecting patients with CRLM who may benefit most from curative liver-directed therapy.

Keywords: Colorectal liver metastasis- preoperative chemotherapy- predictive factor- clinical risk score

Asian Pac J Cancer Prev, **24 (9)**, 3037-3047

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death. (Sung et al.,2021) Liver metastasis is common in approximately 30% of cases (Liu et al., 2016) and is the main reason for mortality in CRC patients. Hepatic resection remains the only curative option and is a well-accepted treatment for colorectal liver metastasis (CRLM). The 5-year survival rate after resection ranges from 37% to 58%. (Viganò et al., 2012; René et al., 2012).

The resection of CRLM in selected patients has been the standard of care for the past 20 years. The median survival is 44 months, and the survival curve plateaus 10 years after hepatic resection, leading to curation in some patients. (Tomlinson et al., 2007) The median 5-year overall survival (OS) ranges from 12% to 41%, and the 10-year OS is 20% (Fernandez et al., 2004). Although liver resection is the gold standard for CRLM, some patients are not a candidate for resection for several reasons. Locoregional treatment modalities, such as cryotherapy and radiofrequency ablation (RFA), are treatment options. A randomized phase II trial showed the benefit of combined systemic chemotherapy with local treatment by RFA with or without liver resection. The 5-year OS rate was 30.3%, and the median OS was 45.6 months (Ruers et al., 2017).

Several studies have shown that preoperative chemotherapy significantly improves survival for

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patients with initially resectable CRLM, especially for those with a high risk of disease recurrence. (Liu et al., 2016; Nordlinger et al., 2008) For patients with borderline resectable CRLM, preoperative systemic chemotherapy improves 3- year and 5-year OS by 80.5% and 66.6%, respectively. (Ichida et al., 2019) Combined preoperative systemic chemotherapy with biologic agents for CRLM was shown to be associated with an objective response rate of 68%. (Hasegawa et al., 2014; Nasti et al., 2013; Folprecht et al., 2010; Sabanathan et al., 2016; Bridgewater et al., 2020) However, the addition of biologic agents to systemic chemotherapy did not improve OS. Several clinical risk scores such as Fong and Nordlinger scores (Fong et al., 1999; Nordlinger et al., 1996), and other predictive factors (Wang et al., 2007) for survivals have been extensively studied in CRLM patients who undergo upfront liver surgery, but not with patients who receive preoperative chemotherapy followed by curative liver surgery.

Recently, a multidisciplinary approach has become the mainstream strategy for CRLM management. The use of preoperative chemotherapy in patients with CRLM has been increasing as it might improve the R0 resection rate, convert tumors from unresectable to resectable, and eradicate occult metastasis. (Adam et al., 2004; Solaini et al., 2019) In addition, predictive factors of CRLM patients who received preoperative systemic chemotherapy and biologic agents were not well established. Our study aimed to identify factors that predicted the benefits of preoperative chemotherapy and biologic agents, optimal dose/duration, clinical risk scores, and toxicity in patients with resectable and borderline resectable CRLM.

Materials and Methods

Patients and study design

This study was a retrospective study. All patients with initially or borderline resectable CRLM who received preoperative systemic chemotherapy and/or biologic agents before undergoing curative surgery and/or local therapy were identified from a Ramathibodi Cancer Registry database and medical records in Ramathibodi Hospital, Mahidol University between 1 January 2012 and 30 December 2018 via ICD-9-CM. Patients who did not receive surgery after preoperative systemic chemotherapy and/or biologic agents, those with pathologically-confirmed non-adenocarcinoma, and patients whose electronic data were unavailable in electronic medical records at Ramathibodi Hospital were excluded.

Patient baseline characteristics, including age, sex, Eastern Cooperative Oncology Group performance status, and comorbidities, were reviewed. Tumor characteristics included the primary tumor site, staging, extrahepatic disease, time between diagnosed primary cancer and CRLM, number of liver metastases, tumor molecular status, plasma carcinoembryonic antigen (CEA) level at liver metastasis diagnosis and post-chemotherapy, recurrence pattern, liver resection margin, and response according to the RECIST version 1.1 (Schwartz et al., 2016) before liver-directed therapy. All imaging studies were reviewed by two independent radiologists. For treatment data, the type of preoperative chemotherapy and biologic agent, chemotherapy regimen, mean cumulative dose of preoperative chemotherapy and biologic agent, duration of preoperative chemotherapy, type of liver-directed therapy, and postoperative chemotherapy used were collected. We categorized preoperative chemotherapy CEA as $<$ or $\geq$ 200 ng/ml, (Fong et al., 1999) the number of liver metastases at diagnosis as $<$ or $\geq$ 3, (Imai et al., 2016) and the cut-off duration and cumulative dose of preoperative chemotherapy as $<$ or $\geq$ 3 months. (Nordlinger et al., 2008; Hasegawa et al., 2014) To identify the optimal cumulative dose of preoperative chemotherapy, we calculated the cumulative dose of each chemotherapy at the cut-off of 3 months, and the cumulative dose of oxaliplatin was consistent with 510 mg/m2 (Nordlinger et al., 2008; Hasegawa et al., 2014; Nasti et al., 2013; Gruenberger et al., 2008) All liver injury patterns were defined from liver histopathology reports. This study was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University.

Clinical risk score

We used the two most referenced clinical risk scores in CRLM, including the Fong and Nordlinger scores (Fong et al., 1999; Nordlinger et al., 1996), to estimate prognosis and oncologic outcomes in our study. The Fong and Nordlinger scores were calculated before patients received preoperative chemotherapy and before liver-directed therapy using definitions from the original publications (Table S1). Patients were divided into two risk groups for the Fong score: a low-risk group with scores of 0–2 and a high-risk group with scores of 3–5. Similarly, patients were divided into two risk groups for the Nordlinger score: a low-risk group with scores of 0–2 and a high-risk group with scores $\geq$ 3. The scores were only calculated in patients with all parameters available. Patients with missing data to complete score calculations were excluded from score analyses. We calculated these clinical risk scores at two time points (before patients received preoperative chemotherapy and before liver-directed therapy). Furthermore, we calculated the differences in scores between the two time points and classified them into two groups (no increase vs. increase) to identify the impact of preoperative chemotherapy on the accuracy of these scores in predicting survival outcomes.

Definitions

Disease-free survival (DFS) was defined as the time from the date of first liver-directed therapy to imaging-confirmed progressive or recurrent disease based on the RECIST criteria version 1.1 or death from any cause, whichever occurred first. (Schwartz et al., 2016) OS was defined as the time from the date of first liver-directed therapy to death from any causes. The synchronicity of liver metastasis was cut off at 6 months; synchronous liver metastasis was defined as liver metastasis diagnosed within 6 months after diagnosis of the primary tumor (Wang et al., 2007; Garajova et al., 2020).

Statistical analysis

The primary objective was to define the factors

that predicted survival outcomes of preoperative chemotherapy and biologic agents, optimal dose, and toxicity in patients with (borderline) resectable CRLM. The secondary objectives were to evaluate the well-known predictive clinical risk scores, including the Fong and Nordlinger scores, in CRLM patients before and after receiving preoperative chemotherapy and/or biologic agents and assess the impact of each clinical risk score on survival outcomes.

All analyses were performed using STATA/MP version 16.1. Descriptive statistical analyses were used where appropriate. Continuous variables were described by mean ± standard deviation (SD) or median (range). Differences between categorical data were compared using the Chi-square or Fisher's exact tests. Survival was estimated using the Kaplan–Meier method and compared by the log-rank test. Uni- and multivariate analyses were performed using Cox regression analysis. A p-value < 0.05 indicated statistically significant differences.

Results

Patient and treatment characteristics

A total of 174 patients with CRLM who underwent liver resection ± local therapy were identified. Nine patients were excluded from this study because liver pathology confirmed that they did not have metastatic adenocarcinoma (one hepatocellular carcinoma, one neuroendocrine, and one tumor invaded liver), and the others received palliative liver directed therapy. Overall, 67 patients received liver-directed surgery upfront (Figure S1). A total of 98 patients were eligible for analysis. The baseline patient and pathological characteristics are summarized in Table 1. The median age at diagnosis of liver metastasis was 59 (30–78) years. Male sex was more predominant than female sex. Almost 90% of patients had synchronous disease. The primary tumor was located in the colon in 69.5% and rectum in 30.5% of cases, and most were left-sided tumors (87.4%). At diagnosis, the median number of liver metastases was two (interquartile range, 1–4). There were 11 patients with extrahepatic metastasis. All RAS mutations were tested in approximately 63%

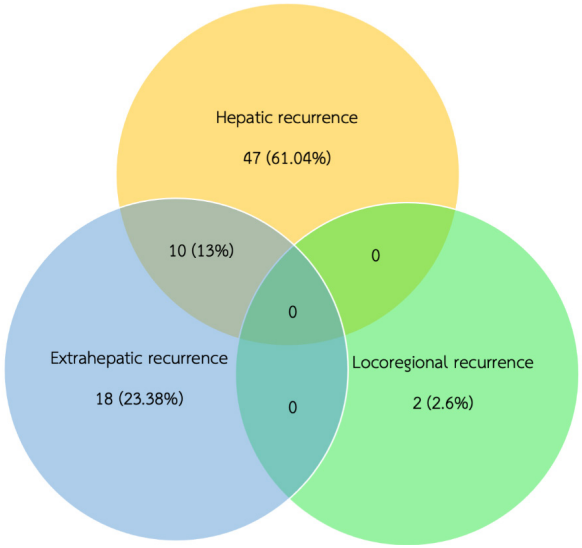

Figure 1. Recurrence Pattern

Table 1. Patients and Pathological Characteristics

Characteristic	Total (n=98) n (% or range)
Median Age, year	59 (30-78)
Gender (n=98)	
Male	69 (70.4)
Female	29 (29.6)
ECOG status (n=75)	
0	44 (58.7)
1	31 (41.3)
Hepatitis B/C infection (n=44)	8 (18.2)
Comorbidity	
HT	37 (38.1)
DM	21 (21.7)
CVS	4 (4.1)
CKD	3 (3.1)
Cirrhosis	3 (3.1)
Primary tumor (n=95)	
Colon	66 (69.5)
Rectum	29 (30.5)
Sideness of the primary tumor (n=95)	
Right side	12 (12.6)
Left side	83 (87.4)
The synchronicity of liver metastasis (n=98)	
Synchronous	88 (89.8)
Metachronous	10 (10.2)
T stage (n=89)	
2	7 (7.9)
3	68 (76.4)
4	14 (15.7)
N stage (n=89)	
0	15 (16.9)
1	34 (38.2)
2	40 (44.9)
Extra-hepatic metastasis (n=93)	11 (11.8)
Number of liver metastasis at diagnosis by CT (n=98)	
< 3	45 (45.9)
≥ 3	53 (54.1)
Tumor Molecular Status (n=62)	
KRAS and/or NRAS mutation	19 (30.7)
BRAF mutation	0
Microsatellite Instability (n=21)	1 (4.8)
RECIST before Liver Directed therapy (n=62)	
CR/PR	29 (46.8)
SD	21 (33.9)
PD	12 (19.3)
Mean CEA at diagnosis of liver metastasis	246 (0.9-4267)
Plasma CEA at diagnosis of liver metastasis (ng/mL) (n=80)	
< 200	66 (82.5)
≥200	14 (17.5)

Table 1. Continued

Characteristic	Total (n=98) n (% or range)
Liver resection margin (n=77)	
R0	63 (81.8)
R1	14 (18.2)
Pre-CMT FONG score (n=83)	
0-2	24 (28.9)
3-5	59 (71.1)
Pre-CMT Nordlinger score (n=79)	
0-2	43 (54.4)
≥2	36 (45.6)

of patients, and 30% had RAS mutation. Only 15% of patients were tested for BRAF mutations, and all of them had BRAF wild-type status.

The Fong and Nordlinger scores were calculated in 83 and 79 patients during the preoperative chemotherapy period, respectively. The percentage of patients with a high-risk Fong score was 71.1%, and those with a high-risk Nordlinger score was 45.6%. Pre-surgery Fong and Nordlinger scores were calculated in 82 and 78 patients, respectively. The proportion of patients with a high-risk pre-surgery Fong score was 56.1%, and that of patients with a high-risk pre-surgery Nordlinger score was 44.9%.

We evaluated responses according to the RECIST criteria version 1.1 before liver-directed therapy. The objective response rate [including complete response (CR) and partial response (PR)] was 46.8%, and one patient achieved CR. The disease control rate (including CR, PR, and stable disease) was 80.7%, whereas 19.3% had disease progression before liver-directed therapy. The proportion of patients who achieved R0 resection was 81.8%.

Systemic treatment and liver-directed therapy

Most patients underwent oxaliplatin-based chemotherapy (72.7%), and 15.9% received both oxaliplatin and irinotecan (Table 2). FOLFOX was the

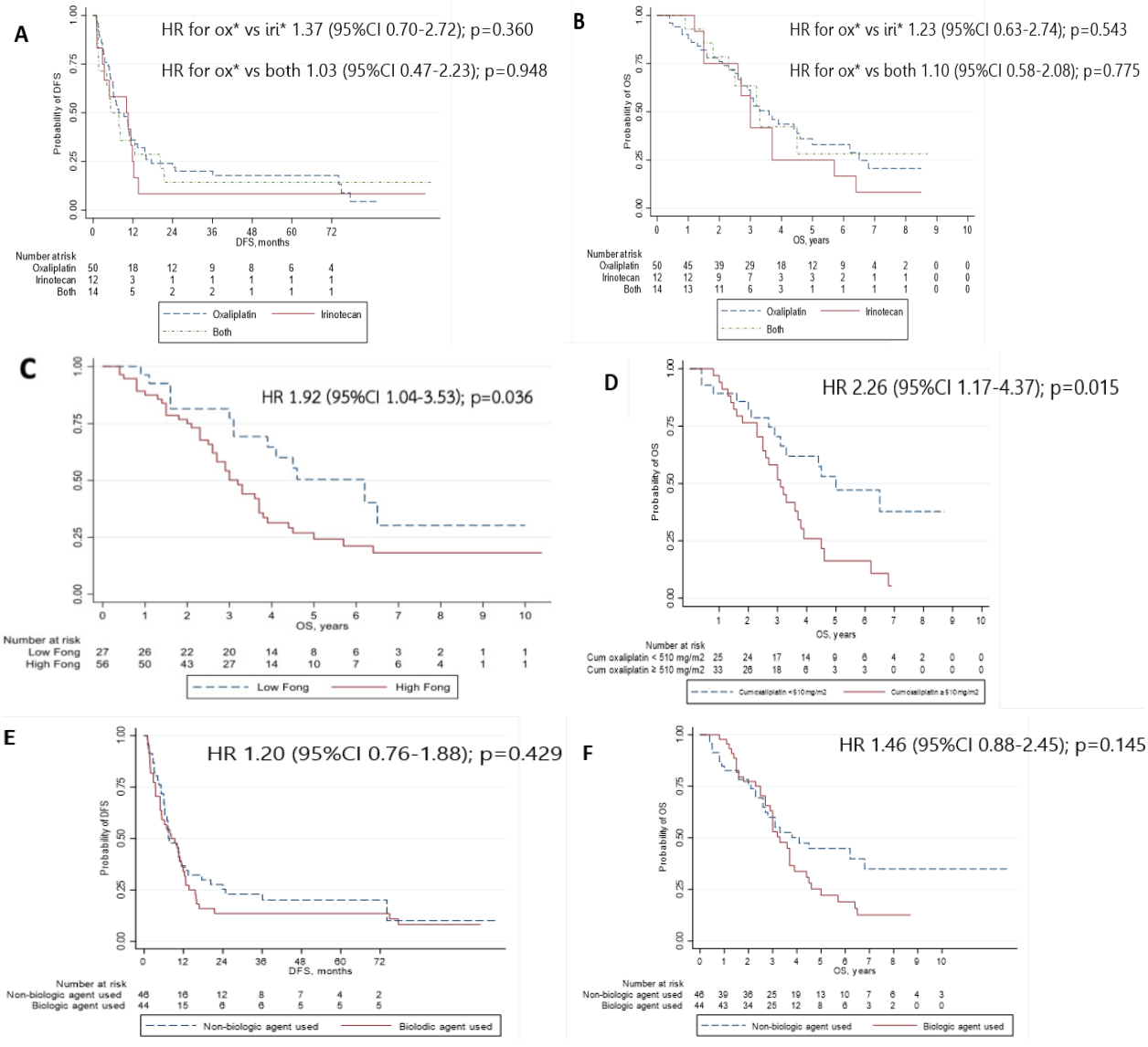

Figure 2. Survival Based on Treatment: DFS of chemotherapy type (A), OS of chemotherapy type (B), DFS of cumulative oxaliplatin group (C), OS of cumulative oxaliplatin group (D), DFS of targeted therapy used group (E), OS of targeted therapy used group (F)

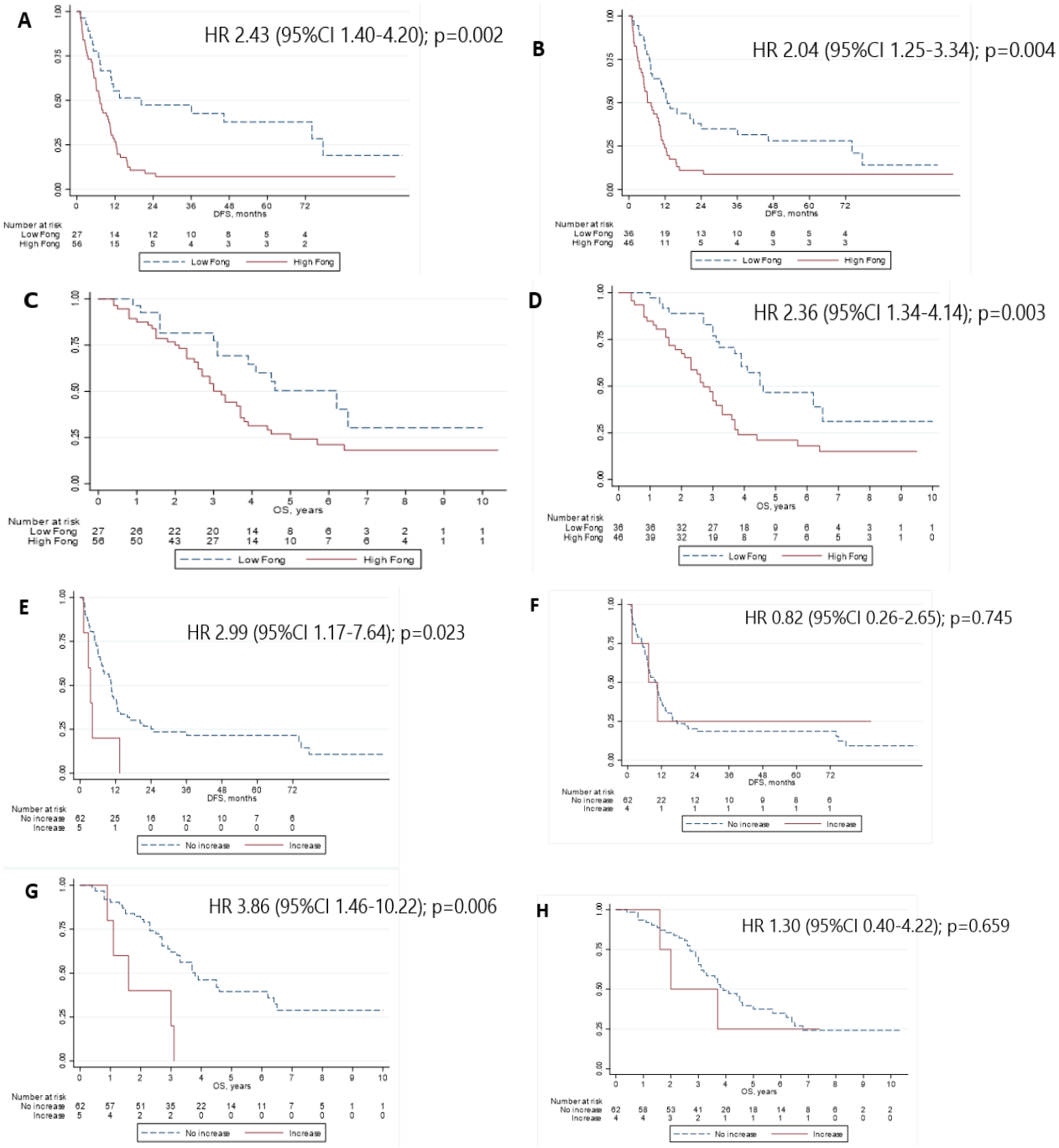

Figure 3. Kaplan-Meier Curve Shows Survival According to Fong and Nordlinger Score Group: DFS of baseline Fong score group (A), DFS of pre-surgery Fong score group (B), OS of baseline Fong score group (C), OS of pre-surgery Fong score group (D), DFS of Fong score changed group (E), DFS of Nordlinger score changed group (F), OS of Fong score changed group (G), OS of Nordlinger score changed group (H)

most common preoperative chemotherapy regimen (55.7%). More than half of patients (66.3%) received preoperative chemotherapy for more than 3 months. Bevacizumab and anti-epidermal growth factor receptor (EGFR) agents were administered in 24.4% and 25.6%, respectively. Postoperative chemotherapy was given in 67.4% of patients in our cohort. The mean cumulative dose of systemic treatment is shown in Table S2. Almost all patients received liver surgery, and 20.6% underwent major hepatectomy. Local therapy, including RFA and microwave ablation, was used in 13.3%. In addition, only 3% of patients received combined liver surgery and local therapy.

Chemotherapy-induced liver injury

A total of 75 of 85 patients who underwent liver resection were reviewed for liver histopathology. Overall, chemotherapy-induced liver injury was observed in 29 of 75 patients (38.7%). Twenty-seven patients (36%) had fatty liver changes, and two patients (2.7%) had sinusoidal obstruction syndrome. The incidence of post-hepatectomy liver failure was 17.9% in our study. The treatment and liver injury data are shown in Table 2. The incidence of chemotherapy-induced liver injury in patients who

Table 2. Treatment and Liver Toxicities

Treatment	Total (n=98) n (% or range)
Type of chemotherapy	
5FU	63 (70)
Capecitabine	27 (30)
Oxaliplatin	64 (72.7)
Irinotecan	26 (28.9)
Both oxaliplatin + irinotecan	14 (15.9)
Chemotherapy Regimen	
FOLFOX	49 (55.7)
CAPEOX	23 (26.1)
FOLFIRI	24 (25)
Bevacizumab	22 (24.4)
Anti-EGFR	23 (25.6)
Biologic agent (n=90)	
No used	46 (51.1)
Used	44 (48.9)
Duration of chemotherapy (n=98)	
≤ 3 months	33 (33.7)
> 3 months	65 (66.3)
Postoperative chemotherapy (n=86)	58 (67.4)
Type of directed liver therapy (n=98)	
Surgery	82 (83.7)
RFA/MWA	13 (13.3)
Surgery + RFA/MWA	3 (3)
Liver toxicities (n=75)	
Fatty liver	27 (36)
Sinusoidal obstruction syndrome	2 (2.7)
Post-hepatectomy liver failure (n=89)	16 (17.9)

received oxaliplatin-based, irinotecan-based, and both was 42.1%, 55.6%, and 20%, respectively. There was no association between chemotherapy type and the presence of liver injury [odds ratio (OR) 1.72, 95% confidence interval (CI) 0.40–7.43, p=0.468]. Similarly, the duration of preoperative chemotherapy was not significantly associated with liver injury (OR 1.71, 95%CI 0.64–4.55, p=0.283). Furthermore, suffering from liver injury was not associated with an increased risk of post-hepatectomy liver failure (OR 2.16, 95%CI 0.64–7.30, p=0.216).

Recurrence pattern and survival outcomes

The median follow-up time of the study was 45.8 months (range 9–159). A total of 77 patients (78.6%) had disease recurrence after liver-directed therapy (Figure 1). The most frequent type was hepatic recurrence (61%), followed by extrahepatic recurrence (23.4%). Ten patients (13%) had both hepatic and extrahepatic recurrence. Only 2.6% of patients had locoregional recurrence.

The median DFS and OS of the overall cohort were 8.7 months and 3.6 years, respectively (Figure S2). The 5-year DFS and OS rates were 17.5% and 32.9%, respectively. In the multivariate Cox regression analysis, the baseline Fong score was associated with DFS [hazard ratio (HR) 2.42, 95%CI 1.14–4.24, p=0.018] but not OS (HR 1.81, 95%CI 0.66–4.99, p=0.247). In contrast, female sex and the type of directed liver therapy were significantly associated with OS (HR 2.43, 95%CI 1.04–5.66, p=0.040 and HR 0.22, 95%CI 0.05–0.96, p=0.044, respectively) (Table 3). However, no significant difference in DFS and OS was found between the primary tumor site, side of the primary tumor, response after preoperative chemotherapy, and duration of preoperative chemotherapy (Figure S3).

DFS and OS were not different between oxaliplatin- and irinotecan-based regimens. The median DFS in the oxaliplatin group was 9.3 months compared with 10.1 months in the irinotecan group (p=0.360), and the median OS was 3.6 vs. 3 years (p=0.543) (Figure 2A and 2B). In the oxaliplatin subgroup, patients who received a cumulative dose of oxaliplatin < 510 mg/m2 showed significantly longer DFS and OS; the median DFS was 11.5 vs. 7.3 months (HR 1.99, 95%CI 1.13–3.48, p=0.017), and the median OS was 5.0 vs. 3.1 years (HR 2.26, 95%CI 1.17–4.37, p=0.015) (Figure 2C and 2D). In contrast, the median OS in patients who received both bevacizumab and anti-EGFR agents was shorter than that in patients who did not receive biologic agents, but the difference was not statistically significant (3.3 vs. 4.1 years, p=0.145) (Figures 2E–F, S3G, and S3H). There were 58 patients (67.4%) in our study who received post-operative chemotherapy, and the DFS in this subgroup was not significantly improved (p=0.065).

Patients with high baseline and pre-surgery Fong scores had significantly shorter DFS and OS than those with low scores (Figure 3A–D). However, only the baseline Nordlinger score was significantly associated with DFS and OS (Figure S5A–D). The changes in Fong and Nordlinger scores were analyzed in 67 and 66 patients, respectively. The change in Fong score between baseline and pre-surgery was significantly associated with both DFS and OS. Patients with an increased Fong score before liver-directed therapy had significantly worse DFS (HR 2.99, 95%CI 1.17–7.64, p=0.023) and OS (HR 3.86, 95%CI 1.44–10.22, p=0.006) (Figure 3E, 3G). In contrast, an increased Nordlinger score was not associated with survival outcomes (Figure 3F, 3H).

Discussion

Our study identified predictive factors and survival outcomes for preoperative chemotherapy in patients with borderline resectable CRLM. The median DFS, OS, and 5-year OS rates in this study were comparable to those in the literature (Kim et al., 2019; Adam et al., 2001). The most common type of disease recurrence in our study was intrahepatic recurrence (61%), which was relatively higher than that reported in a previous study, potentially because of poorer baseline clinical and pathological characteristics (Kim et al., 2019). Predictive factors for preoperative chemotherapy in CRLM patients were previously defined with varying results. However, the most effective predictive factors for oncological outcomes were age, primary tumor N stage, and extrahepatic metastasis (Imai et al., 2016; Kim et al., 2019; Acciuffi et al., 2018). In our study, we demonstrated that patients who underwent

Table 3. Univariate and Multivariate Analysis for DFS and OS

Variable	DFS						OS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95%CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age ≥65	1.48	0.93-2.32	0.091				1.83	1.11-3.01	0.018	0.99	0.95-1.04	0.837
Female	1.75	1.10-2.78	0.017	1.34	0.73-2.49	0.347	2.05	1.24-3.40	0.005	2.43	1.04-5.66	0.04
ECOG PS	0.99	0.61-1.65	0.995				1.01	0.57-1.80	0.963			
Hepatitis B/C infection	0.68	0.26-1.76	0.43				0.7	0.21-2.38	0.571			
Primary tumor												
colon	Ref						Ref					
Rectum	1.35	0.64-2.87	0.429				1.55	0.68-1.94	0.606			
Sideness of primary tumor												
Right	Ref						Ref					
Left	1.38	0.66-2.87	0.389				1.48	0.64-0.43	0.365			
T stage												
1-2	Ref						Ref					
3-4	1.94	0.71-5.31	0.197				1.91	0.50-6.10	0.275			
N stage												
0	Ref						Ref					
1	1.7	0.82-3.52	0.154				1.64	0.76-3.55	0.211			
2	2.94	1.45-5.97	0.003				1.76	0.82-3.76	0.144			
Synchronous liver metastasis	1.19	0.59-2.39	0.625				0.72	0.36-1.46	0.364			
Extra-hepatic metastasis	1.54	0.81-2.93	0.186				2.1	1.02-4.30	0.044	0.9	0.20-4.00	0.893
Number of liver metastasis at diagnosis												
< 3	Ref						Ref					
≥3	1.4	0.90-2.17	0.131				1.22	0.75-1.99	0.425			
KRAS and/or NRAS mutation	1.26	0.70-2.27	0.44				2.33	1.22-4.45	0.011	1.39	0.55-3.48	0.484
Pre CMT CEA (ng/ml)												
< 200	Ref						Ref					
≥ 200	1.47	0.78-2.75	0.227				1.57	0.79-3.13	0.201			
RECIST before Liver Directed therapy												
Non-PD	Ref						Ref					
PD	0.81	0.46-1.44	0.478				1.04	0.54-1.99	0.914			

Table 3. Continued

Variable	DFS						OS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95%CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Type of preoperative chemotherapy												
Oxaliplatin-based	Ref						Ref					
Irinotecan-based	1.23	0.63-2.39	0.543				1.37	0.70-2.72	0.36			
Both	1.1	0.58-2.08	0.775				1.03	0.47-2.23	0.948			
Duration of preoperative chemotherapy												
< 3	Ref						Ref					
≥3	1.26	0.79-2.00	0.33				0.98	0.58-1.63	0.925			
Cumulative oxaliplatin												
< 510 mg/m2	Ref			Ref			Ref			Ref		
≥ 510 mg/m2	1.99	1.13-3.48	0.017	1	1.00-1.00	0.09	2.26	1.17-4.37	0.015	1	0.99-1.00	0.218
Biologic agent used	1.2	0.76-1.88	0.429				1.46	0.88-2.45	0.145			
Postoperative chemotherapy	0.63	0.39-1.03	0.065				0.74	0.42-1.28	0.285			
Type of directed liver therapy												
No liver surgery	Ref			Ref			Ref					
Liver surgery	0.55	0.30-1.00	0.05	0.48	0.21-110	0.084	0.36	1.90-0.69	0.002	0.22	0.05-0.96	0.044
R1 liver resection	1.32	0.68-2.53	0.412				1.26	0.58-2.71	0.557			
Pre-CMT Fong score												
Low	Ref			Ref			Ref			Ref		
High	2.42	1.40-4.20	0.002	2.2	1.14-4.24	0.018	1.92	1.04-3.53	0.036	1.81	0.66-4.99	247
Post-hepatectomy liver failure	1.14	0.64-2.04	0.662				1.17	0.62-2.22	0.619			

liver resection had longer DFS and OS than those who received other local therapy alone, consistent with a previous meta-analysis (van Amerongen et al., 2017).

Currently, prospective studies with head-to-head comparisons for the role of preoperative chemotherapy in CRLM are limited, and most prospective studies have investigated the combination of perioperative chemotherapy and surgery. As a result, the optimal dose and duration of preoperative chemotherapy remain unknown. Several studies planned preoperative chemotherapy for 3 months (Hasegawa et al., 2014; Nasti et al., 2013; Gruenberger et al., 2008). In the EORTC 40983 trial (Nordlinger et al., 2008), the duration of preoperative FOLFOX was 3 months (six cycles), with a 92% relative-dose intensity. The current study aimed to identify the optimal cumulative dose of preoperative chemotherapy. We demonstrated that the cumulative dose of oxaliplatin was associated with DFS and OS, and patients who received > 510 mg/m2 oxaliplatin had worse outcomes. This was consistent with the duration of preoperative chemotherapy of 3 months. However, our study might contain selection bias because patients with favorable responses may receive less preoperative chemotherapy.

The use of biologic agents, especially anti-EGFR drugs, in addition to preoperative chemotherapy in patients with initially unresectable or potentially resectable CRLM is not associated with improved survival outcomes. In addition, no phase 3 studies have evaluated the efficacy of bevacizumab added to standard chemotherapy in this setting. Most previous data demonstrated that anti-EGFR drugs increased response and resectability rates but not survival (Hasegawa et al., 2014; Nasti et al., 2013; Folprecht et al., 2010; Gruenberger et al., 2008). A long-term follow-up phase 3 study of preoperative mFOLFOX6 with or without cetuximab (New EPOC trial) in patients with KRAS wild-type (codons 12, 13, and 61) resectable CRLM demonstrated a significant disadvantage in terms of DFS for patients treated with cetuximab. (Hasegawa et al., 2014) Thus, the addition of biologic agents for patients with CRLM was considered detrimental. In our study, we demonstrated that the OS of patients who received biologic agents, both anti-EGFR and bevacizumab, did not improve and tended to be worse, which was consistent with the literature.

The overall incidence and outcomes of chemotherapy-induced liver injury in our study were consistent with those reported in the literature (Chow and Chok et al., 2019). There are two major pathological patterns in chemotherapy-induced liver injury: steatohepatitis and sinusoidal injury. The oxaliplatin-based regimen significantly increases the risk of sinusoidal injury, whereas the irinotecan-based regimen is more associated with steatohepatitis (Viganò et al., 2013; Gangi and Lu., 2020). However, we observed only two patients whose pathology was reported as sinusoidal injury. Thus, the associations between each chemotherapy regimen and liver injury subtype were not analyzed. Because our study was limited by the retrospective design, the incidence of baseline steatohepatitis or sinusoidal injury before chemotherapy from other causes was unknown. The association between the duration of preoperative chemotherapy and liver injury is controversial. In our study, a longer duration of preoperative chemotherapy was not associated with an increased risk of chemotherapy-induced liver injury, which was consistent with a report from Tamandl et al (Tamandl et al., 2011). However, two other studies demonstrated that receiving > 6 cycles (3 months) of preoperative chemotherapy significantly increased the risk of liver injury (Viganò et al., 2013; Gangi and Lu., 2020).

Currently, the role of postoperative chemotherapy after liver resection is controversial. The JCOG0603 study showed that adjuvant mFOLFOX6 after hepatectomy in CRLM improved PFS, but this did not translate to prolonged OS (Kanemitsu et al., 2021). Conversely, the results of a pooled analysis of two randomized controlled trials did not support the use of adjuvant chemotherapy after curative liver resection in CRLM (Mitry et al., 2008). In our study, a subgroup of patients who received postoperative chemotherapy showed a trend toward improved PFS outcomes.

Several clinical risk scores predicting the outcomes of patients with CRLM who underwent curative liver surgery have been extensively studied. The Fong and Nordlinger scores are the most referenced (Schreckenbach et al., 2015; Wimmer et al., 2016). However, these scores were established for patients with CRLM who undergo upfront curative liver surgery. The impact of postoperative chemotherapy and/or biologic agents on the accuracy of these clinical risk scores after chemotherapy remains unknown. A previous retrospective study of 117 CRLM patients who received preoperative chemotherapy followed by liver resection showed that the Fong and Nordlinger scores calculated prior to liver resection did not predict OS (Schreckenbach et al., 2015). In contrast, our study demonstrated that both scores calculated at baseline prior to preoperative chemotherapy administration maintained significance in predicting survivals. The outcomes of our study differed from the previous study (Schreckenbach et al., 2015), which might be partially explained by higher incidence of patients with high-risk scores in our study when compared with the previous report. In addition, increased Fong scores but not Nordlinger scores after preoperative chemotherapy in our study were significantly associated with worse DFS and OS, which was consistent with the literature (Wimmer et al., 2016).

Our study contained several limitations because of the retrospective study design. Since we included only patients who underwent liver resection and/or local therapy, patients who received preoperative chemotherapy but did not undergo curative surgery for any reasons were not included in this study. Approximately 13% of patients had incomplete chemotherapy data as some patients received chemotherapy at other hospitals but were referred to our hospital for liver resection.

In conclusion, Although preoperative chemotherapy in CRLM offers the chance of long-term survival, valuable tools to estimate the oncologic outcomes of patients undergoing preoperative treatment are still limited. In our study, the Fong clinical risk score, female sex, and liver surgery as a part of liver-directed therapy were

independent prognostic factors for survival, whereas the type and cumulative dose of chemotherapy and use of biological agents were not. Chemotherapy-induced liver injury was commonly observed in our study. These clinical factors should be considered as an option to guide physicians' decisions in selecting patients with CRLM who may benefit most from curative liver-directed therapy.

Author Contribution Statement

Study concepts: NI, NN. Study design: NI, NN. Data acquisition: NI, PS, NA, MA, TS. Quality control of data and algorithms: NI, NN. Data analysis and interpretation: All authors. Statistical analysis: NI, NN. Manuscript preparation: NI, NN. Manuscript editing: All authors. Manuscript review: All authors. All authors have read and approved the manuscript..

Acknowledgements

Ethical Approval

This study was approved by the Ramathibodi Ethics Committee of Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (EC ID# COA. MURA2021/115).

Availability of data and materials

All analyzed and derivative raw data are available on request.

Conflict of Interest

N. Ngamphaiboon reports institutional research funding from Pfizer, MSD, Roche, Exelixis, RAPT therapeutics, BeiGene, and Boehringer Ingelheim Pharmaceuticals; and personal fees and nonfinancial support from MSD, Roche, Merck, AstraZeneca, Novartis, Eli-Lilly, and Bayer. The other authors declare no conflict of interest.

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