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ORIGINAL SCIENTIFIC REPORT

Hepatectomy for Colorectal Cancer Liver Metastases in the Era of Modern Preoperative Chemotherapy: Evaluation of Postoperative Complications

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Abstract

Background Recently, an increasing number of patients with liver metastases from colorectal cancer have received chemotherapy before hepatectomy. However, the effect of chemotherapy on postoperative short-term outcome is not well defined.

Methods We retrospectively investigated the postoperative complications of 439 patients who underwent hepatectomy for colorectal liver metastases in our division from 2005 to 2014. Patients were classified into two groups according to the presence (Cx; 84 patients) or absence (NCx; 355 patients) of preoperative chemotherapy. Univariate and multivariate analyses were conducted to determine the predictive factors for postoperative complications.

Results There was neither mortality nor liver failure after surgery. There was no significant difference in the frequency of postoperative complications between Groups Cx and NCx [29 vs 26 % for all complications; both 6 % for bile leakage that required therapeutic intervention; and 2 vs 3 % for Clavien–Dindo (CD) Grade $\geq$ IIIa, respectively]. In Group Cx, morbidity rates were similar among patients with different chemotherapy regimens. Chemotherapy-related factors (administration of bevacizumab, oxaliplatin or irinotecan, duration of chemotherapy >150 days, and timing of hepatectomy) were not significantly associated with clinically relevant bile leakage and CD $\geq$ IIIa in multivariate analysis.

Conclusion Even after combination chemotherapy including targeted therapy, hepatectomy for colorectal liver metastases can be performed safely without increasing morbidity or mortality, if the patients fulfill the conventional criteria for surgery.

Introduction

Every year, >1.3 million patients are newly diagnosed with colorectal cancer (CRC) and about 700,000 patients are estimated to die of the disease worldwide [1]. In Japan, the incidence of CRC has increased twofold in the last two decades [2] and it was estimated to become the second leading cause of cancer death in 2015 [3].

Up to 50 % of patients with CRC develop liver metastases [4, 5]. Hepatectomy is the only potentially curative treatment for colorectal liver metastasis (CRLM), and 5-year survival rates after resection are 35–60 % [4, 6]. However, >80 % of patients are not amenable to liver

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resection because of advanced disease at the time of diagnosis [4, 5].

Systemic chemotherapy is usually administered to patients with unresectable CRLMs, and recent advances in chemotherapy have significantly prolonged survival [5]. Furthermore, effective chemotherapy has extended the chance of surgical resection for initially unresectable CRLMs by reducing the size and numbers of tumors [7, 8]. Improved disease-free survival after hepatectomy is also reported with perioperative chemotherapy for resectable CRLMs [9]. Therefore, an increasing number of patients have undergone chemotherapy and subsequent hepatectomy recently.

However, the adverse effects of preoperative chemotherapy on the normal liver parenchyma may be associated with increased morbidity and mortality after hepatectomy [7, 9–11]. The safety of hepatectomy after preoperative chemotherapy has not been fully investigated, especially in Asian populations.

Oxaliplatin causes sinusoidal obstruction syndrome (SOS) [10–12], and irinotecan is associated with steatohepatitis [7, 10]. Recently, molecular targeted drugs such as bevacizumab (BV), cetuximab, or panitumumab have often been added to oxaliplatin- or irinotecan-based regimens. It is reported that BV improves pathological response of the tumor and protects against SOS caused by oxaliplatin-containing chemotherapy [13, 14]. However, the possibility of delayed wound healing or impaired hepatic regeneration caused by blockage of vascular endothelial growth factor is of great concern [15, 16].

The aims of this study were: (1) to investigate whether preoperative chemotherapy was associated with an increased rate of postoperative complications compared with no chemotherapy; (2) to analyze whether BV-containing chemotherapy influenced the morbidity rate after hepatectomy; and (3) to investigate the predictive factors for post-hepatectomy complications in patients who underwent preoperative chemotherapy for CRLMs.

Methods

Patients

All consecutive patients who underwent hepatectomy for CRLM at the National Cancer Center Hospital, Tokyo, Japan, between January 2005 and April 2015 were identified in our prospectively maintained database. The study was conducted under the approval of our institutional review board and complied with the principles of the Declaration of Helsinki.

Preoperative chemotherapy was defined as being administered within 24 weeks before hepatectomy [17, 18]. Patients were categorized into two groups: Cx comprised patients who underwent preoperative chemotherapy; and NCx comprised those who had no preoperative chemotherapy. Group Cx was further divided into the following three groups according to preoperative chemotherapy regimens: Cx-BV: fluoropyrimidine-based regimens + oxaliplatin or irinotecan + bevacizumab; Cx-OI: fluoropyrimidine-based regimens + oxaliplatin or irinotecan; and Cx-M (miscellaneous chemotherapy): fluoropyrimidine-based regimens only.

Analyzed clinical variables

We retrospectively collected clinicopathological data from each patient's medical records, including age, gender, blood test results, resectability status, the size and numbers of CRLMs, extent of liver resection, information on preoperative chemotherapy, and the occurrence of postoperative complications. The extent of hepatectomy was described according to Brisbane 2000 nomenclature [19], and major hepatectomy was defined as the anatomical resection of $\geq$2 sections.

Definition of postoperative complications

Postoperative complications were evaluated according to the international grading system of bile leakage [20], liver failure [21], and the Clavien–Dindo (CD) classification [22]. Liver failure was defined as an increased international normalized ratio and concomitant hyperbilirubinemia on or after postoperative day 5. Bile leakage was diagnosed when bilirubin concentration in the drainage fluid was $\geq$3 times the serum bilirubin level on or after postoperative day 3. Grade A, B, and C bile leakage required no change in clinical management, active therapeutic intervention but no relaparotomy, and relaparotomy, respectively.

Operative indications

All patients underwent preoperative examination of the chest, abdomen, and pelvis by contrast-enhanced computed tomography, ultrasonography, and/or magnetic resonance imaging to assess the size, number, and location of CRLMs and to identify extrahepatic metastases. The indications for hepatectomy were determined at a multidisciplinary conference. Hepatectomy for CRLMs was indicated when: (1) complete resection of the CRLMs was possible, securing sufficient future liver remnant (FLR) volume; and (2) there was no primary tumor or extrahepatic metastases that could not be resected [23]. The sufficient FLR volume was determined based on indocyanine green retention rate at 15 min after injection (ICG-15R), which was similar to the resection criterion for hepatocellular carcinoma [24]. In

patients with normal liver function, approximately 30 % of FLR volume was considered to be sufficient to perform hepatectomy. In cases of small FLR or impaired liver function, percutaneous transhepatic portal embolization (PTPE) was used to prompt FLR hypertrophy [25].

In principle, if the tumor was resectable, hepatectomy was performed without preoperative chemotherapy. However, some patients with resectable CRLM received several courses of chemotherapy before referral to our hospital, or as adjuvant chemotherapy after primary CRC resection.

If the tumor was considered to be unresectable, systemic chemotherapy was administered and the resectability was re-examined every 3–4 months. Chemotherapy regimens were selected at the discretion of the attending physician, considering each patient's tumor and performance status. If the tumor showed partial response and became resectable, hepatectomy was performed. When the tumor was still considered to be unresectable, chemotherapy was continued and computed tomography was repeated at 3- to 4-month intervals.

Table 1 Preoperative chemotherapy regimens

Groups	*n*
Group Cx-BV	32
FOLFOX + BV	14
FOLFIRI + BV	2
FOLFOX + BV → FOLFIRI + BV	3
FOLFOX → FOLFIRI + BV	2
FOLFIRI → FOLFOX + BV	1
FOLFOX + BV → 5FU + LV + BV	4
IRIS + BV	3
XELOX + BV	2
FOLFOX + BV → 5FU + LV + BV → capecitabine + BV	1
Group Cx-OI	17
FOLFOX	8
FOLFIRI	1
FOLFOX → FOLFIRI	3
FOLFIRI → FOLFOX	1
S1 → FOLFOX	1
SOX	1
XELOX	1
5FU + oxaliplatin	1
Group Cx-M	35
5FU + LV	8
UFT + LV	7
UFT	7
Capecitabine	6
S1	4
S1 + CDDP	1
5FU	1
5-DFUR	1

Group Cx-BV: fluoropyrimidine-based regimens + oxaliplatin or irinotecan + BV; Group Cx-OI: fluoropyrimidine-based regimens + oxaliplatin or irinotecan; Group Cx-M: fluoropyrimidine-based regimens only

BV bevacizumab, *IRIS* irinotecan + S1, *LV* leucovorin, *SOX* S1 + oxaliplatin, *XELOX* capecitabine + oxaliplatin

Histological evaluation

We retrospectively reviewed pathological reports of all the patients, and the presence or absence of steatosis, steatohepatitis, and severe SOS of the nontumorous liver in the resected specimen was recorded for each patient. Severity of steatosis or SOS was evaluated according to previous reports [26, 27].

Conducted analysis

We compared the clinicopathological characteristics and postoperative complication rates between Groups Cx and NCx, and among Groups Cx-BV, Cx-OI, and Cx-M. In addition, predictive factors of postoperative complications were investigated in Group Cx.

Statistical analysis

Continuous data were presented as the medians with ranges. For comparison of nonparametric variables, the Mann–Whitney *U* test or Kruskal–Wallis test was used. Differences between categorical variables were evaluated using the Chi-square test or Fisher's exact test, as appropriate. Variables that reached significance in univariate analysis were included in multivariate logistic regression analysis (stepwise backward selection method). A $p < 0.05$ was considered to be statistically significant. The statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

Results

Patient and tumor characteristics

The study population consisted of 439 patients, excluding patients who underwent preoperative chemotherapy including cetuximab ($n = 2$) or panitumumab ($n = 3$). There were 274 men and 165 women, with a median age of 62 years. The CRLMs were synchronous in 137 patients (31 %), multiple in 204 patients (47 %), and the median size of the largest tumor was 2.7 cm. Sixty-two (14 %) and 152 (35 %) patients underwent major and multiple hepatectomy, respectively. In 109 patients (25 %), the operation was repeat hepatectomy. One hundred and twelve (26 %)

Table 2 Lists of postoperative complications

Postoperative complications	*n*	Clavien–Dindo classification [22]						
		I	II	IIIa	IIIb	IVa	IVb	V
Wound complication	21 (5 %)	19	2	0	0	0	0	0
Bile leakage [20]	62 (14 %)							
Grade A	36 (8 %)	36	0	0	0	0	0	0
Grade B	26 (6 %)	0	18	8	0	0	0	0
Grade C	0	0	0	0	0	0	0	0
Intra-abdominal infection unrelated to bile leakage	7 (2 %)	0	4	3	0	0	0	0
Miscellaneous complications	40 (9 %)							
Hepatobiliary	2	1	1	0	0	0	0	0
Cardiovascular	3	1	2	0	0	0	0	0
Pulmonary	7	1	3	1	0	2	0	0
Gastrointestinal	13	6	6	0	0	1	0	0
Urological	4	2	2	0	0	0	0	0
Cerebrovascular	1	0	0	0	0	1	0	0
Infectious	5	2	3	0	0	0	0	0
Others	5	4	0	1	0		0	0
Total	130	69 (16 %)	34 (8 %)	10 (2 %)	0	3 (1 %)	0	0

and five (1 %) patients underwent simultaneous colorectal and pulmonary resection, respectively.

Preoperative chemotherapy regimens

Eighty-four patients underwent preoperative chemotherapy (Group Cx), and 355 patients did not (Group NCx). There were 32, 17, and 35 patients in Groups Cx-BV, Cx-OI, and Cx-M, respectively. The details of chemotherapy regimens are shown in Table 1. Twenty-nine patients received preoperative chemotherapy as adjuvant treatment for primary CRC. Among the other 55 patients who underwent preoperative chemotherapy, initially unresectable CRLMs were converted to resectable after chemotherapy (median duration: 254 days, range: 77–1309 days) in 15 patients.

Postoperative complications

One hundred and thirty postoperative complications occurred in 116 patients (26 %; (Tables 2, 6; see Electronic Supplementary Material). Neither postoperative in-hospital death nor liver failure occurred in Groups Cx and NCx.

Comparison between groups Cx and NCx

ICG-R15, tumor number, and intraoperative blood loss were higher, and operation time was longer in Group Cx than Group NCx (Table 3). Synchronous CRLMs, simultaneous colorectal resection, and major or multiple hepatectomies were more common in Group Cx compared to Group NCx. However, there were no significant differences in the rates of postoperative complications between Groups Cx and NCx, and postoperative in-hospital stay was similar in both groups (Table 3).

Comparison among group Cx-BV, Cx-OI and Cx-M

Although the rate of complications of CD $\geq$ I was higher in Groups Cx-OI and Cx-BV compared with Group Cx-M, there was no significant difference in the rate of bile leakage Grade $\geq$ B, complications of CD $\geq$ IIIa, and postoperative in-hospital stay among Groups Cx-BV, Cx-OI, and Cx-M (Table 4).

Histological evaluation

Pathologically, steatosis was observed in 146 patients (33 %). In most of them, the extent of steatosis was mild to moderate, and only four patients (1 %) showed severe steatosis. Steatohepatitis and severe SOS were found in 37 (8 %) and three (1 %) patients, respectively. Steatosis and SOS were more common in Group Cx compared with Group NCx (Table 3), but there was no significant difference in the rate of steatosis, steatohepatitis, and SOS among Groups Cx-BV, Cx-OI, and Cx-M (Table 4).

Predictive factor of postoperative complications in group Cx

The results of univariate analyses for predictive factors for the occurrence of CD $\geq$ I, bile leakage Grade $\geq$ B, and

Table 3 Comparison of patient characteristics between Groups Cx and NCx

Groups	Cx ($n = 84$, 19 %)	NCx ($n = 355$, 81 %)	p
Age (years)	61 (35–77)	62 (22–91)	0.086
Male	54 (64 %)	220 (62 %)	0.694
BMI (kg/m^2)	22.3 (15.6–33.5)	21.6 (12.9–39.0)	0.229
Diabetes mellitus	10 (12 %)	47 (13 %)	0.743
Albumin (g/dL)	4.3 (3.2–5.0)	4.2 (2.4–5.2)	0.139
ICG-R15 (%)	7.4 (0.4–24)	5.8 (0.1–26)	0.003
CEA (ng/ml)	12.4 (0.7–2420)	9.8 (0.8–4610)	0.212
CA19-9 (U/ml)	29.0 (0–5820)	25.0 (0–9470)	0.158
PTPE	10 (12 %)	13 (4 %)	0.002
Repeat hepatectomy	18 (21 %)	91 (26 %)	0.422
Synchronous (vs metachronous)	16 (19 %)	121 (34 %)	0.007
Simultaneous colorectal resection	6 (7 %)	106 (30 %)	<0.001
Duration of chemotherapy (days)	187 (35–1577)	–	
Interval duration between chemotherapy and hepatectomy (day)	56 (15–160)		
Tumor numbers	2 (1–13)	1 (1–20)	<0.001
Solitary metastasis	30 (36 %)	205 (58 %)	<0.001
Tumor size (cm)	3.0 (0.2–13)	2.7 (0.5–16)	0.136
Major hepatectomy	21 (25 %)	41 (12 %)	0.001
Multiple hepatectomies	40 (48 %)	112 (32 %)	0.005
Intraoperative blood loss (ml)	675 (62–3400)	437 (4–3624)	<0.001
RBC transfusion	7 (8 %)	11 (3 %)	0.058
FFP transfusion	2 (2.4 %)	3 (0.8 %)	0.245
Operation time (minutes)	306 (89–594)	285 (95–680)	0.021
Postoperative in-hospital stay (days)	10 (5–44)	11 (6–42)	0.319
Steatosis	41 (49 %)	105 (30 %)	<0.001
Steatohepatitis	9 (11 %)	28 (8 %)	0.402
Severe SOS	3 (4 %)	0	0.007
CD $\geq$ I	24 (29 %)	91 (26 %)	0.582
Bile leakage Grade $\geq$ B	5 (6 %)	21 (6 %)	0.990
CD $\geq$ IIIa	2 (2 %)	11 (3 %)	0.727

BMI body mass index, *Cx* chemotherapy, *PTPE* percutaneous transhepatic portal embolization, *ICG-R15* indocyanine green retention rate at 15 min after injection, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *RBC* red blood cell, *FFP* fresh frozen plasma, *SSI* surgical site infection, *CD* $\geq$ *I* complications of Clavien–Dindo grade I or higher, *CD* $\geq$ *IIIa* complications of Clavien–Dindo grade IIIa or higher, *SOS* sinusoidal obstruction syndrome

CD $\geq$ IIIa are shown in Tables 5, 7, 8, and 9 (see Electronic Supplementary Material).

In multivariate analysis, Group Cx-BV or Cx-OI and chemotherapy duration >150 days were independent predictive for CD $\geq$ I (Table 5). However, no chemotherapy-related variables were associated with the occurrence of clinically relevant postoperative complications such as bile leakage Grade $\geq$ B or CD $\geq$ IIIa in Group Cx (Table 5).

Even if patients who underwent preoperative chemotherapy in adjuvant setting ($n = 29$) were excluded in the analysis, no chemotherapy-related variables were associated with the occurrence of CD $\geq$ I, bile leakage Grade $\geq$ B, and CD $\geq$ IIIa in multivariate analysis (Table 10; see Electronic Supplementary Material).

Discussion

Chemotherapy has prolonged the prognosis of patients with CRLMs and has become more commonly used in clinical practice. However, several types of chemotherapy-related liver injury (chemotherapy-associated steatohepatitis [28] and SOS [12]) are known to occur after long-term administration, and it is of concern that such

Table 4 Comparison of patient characteristics among Groups CX-BV, CX-OI, and CX-M

Groups	Cx-BV ($n = 32$, 38 %)	Cx-OI ($n = 17$, 20 %)	Cx-M ($n = 35$, 42 %)	p
Age (years)	63 (43–76)	64 (43–75)	57 (35–77)	0.044
Male	17 (53 %)	14 (82 %)	23 (66 %)	0.123
BMI (kg/m^2)	21.8 (16.6–33.5)	23.7 (16.2–32.0)	22.4 (15.6–31.6)	0.317
Diabetes mellitus	4 (13 %)	2 (12 %)	4 (11 %)	0.991
Albumin (g/dL)	4.3 (3.3–4.7)	4.2 (3.3–4.7)	4.3 (3.3–4.9)	0.757
ICG-R15 (%)	7.0 (2.2–22.4)	7.8 (0.6–23.9)	6.0 (0.4–17.1)	0.878
CEA (ng/ml)	9.1 (0.7–1684)	22.8 (1.8–943)	12.4 (1.8–2420)	0.024
CA19-9 (U/ml)	21 (0–1713)	56 (0–5820)	37 (0–1852)	0.028
PTPE	3 (9 %)	2 (12 %)	5 (14 %)	0.825
Repeat hepatectomy	12 (38 %)	4 (24 %)	2 (6 %)	<0.006
Synchronous (vs metachronous)	6 (19 %)	7 (41 %)	3 (9 %)	0.019
Simultaneous colorectal resection,	3 (9 %)	3 (18 %)	0	0.056
Initially unresectable (vs resectable)	11 (34 %)	4 (24 %)	0	0.001
Regimen				<0.001
Oxaliplatin-based	21 (66 %)	12 (71 %)	0	
Irinotecan-based	5 (16 %)	1 (6 %)	0	
Both included	6 (19 %)	4 (24 %)	0	
Both not included	0	0	35 (100 %)	
Duration of chemotherapy (days)	180 (62–1577)	250 (35–1309)	181 (35–777)	0.123
Interval duration between chemotherapy and hepatectomy (day)	54 (19–141)	67 (26–150)	63 (15–160)	0.241
Numbers of BV administration	10 (1–67)			
Days of BV administration (days)	176 (1–1170)			
Interval duration between the final BV administration and hepatectomy (days)	57 (25–158)			
Tumor numbers	2 (1–13)	4 (1–7)	2 (1–12)	0.349
Tumor size (cm)	2.5 (0.5–10.4)	3.9 (1.8–7.0)	3.1 (1.5–12.5)	0.007
Major hepatectomy	5 (16 %)	7 (41 %)	9 (26 %)	0.144
Multiple hepatectomies	15 (47 %)	8 (47 %)	17 (49 %)	0.989
Intraoperative blood loss (ml)	494 (62–2628)	1017 (212–3400)	657 (78–3128)	0.002
Operation time (minutes)	300 (126–594)	383 (155–540)	310 (89–580)	0.058
Postoperative in-hospital stay (days)	10 (7–44)	12 (8–21)	10 (5–24)	0.067
Steatosis	16 (50 %)	9 (53 %)	16 (46 %)	0.874
Steatohepatitis	2 (6 %)	1 (6 %)	6 (17 %)	0.273
Severe SOS	1 (3 %)	1 (6 %)	1 (3 %)	0.846
CD $\geq$ I	9 (28 %)	9 (53 %)	6 (17 %)	0.027
Bile leakage Grade $\geq$ B	3 (9 %)	1 (6 %)	1 (3 %)	0.530
CD $\geq$ IIIa	1 (3 %)	0	1 (3 %)	0.769

Group Cx-BV: fluoropyrimidine-based regimens + oxaliplatin or irinotecan + BV; Group Cx-OI: fluoropyrimidine-based regimens + oxaliplatin or irinotecan; Group Cx-M: fluoropyrimidine-based regimens only

BV bevacizumab, *BMI* body mass index, *PTPE* percutaneous transhepatic portal embolization, *ICG-R15* indocyanine green retention rate at 15 min after injection, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CD* $\geq$ *I* complications of Clavien–Dindo grade I or higher, *CD* $\geq$ *IIIa* complications of Clavien–Dindo grade IIIa or higher, *SOS* sinusoidal obstruction syndrome

chemotherapy-induced liver injury may increase perioperative morbidity.

The association between preoperative chemotherapy and postoperative complications after hepatectomy is still controversial. Several authors have reported that the complication rates of hepatectomy were significantly elevated after preoperative chemotherapy [9, 18, 29, 30]. Nordlinger et al. [9] reported in their randomized trial that perioperative chemotherapy was associated with increased morbidity. However, others reported no increase in

Table 5 Univariate and multivariate analyses of predictive factors of postoperative complications in Group Cx

Variables	Univariate	Multivariate	
	p	Odds ratio (95 % confidence interval)	*p*
All complications (CD ≥ I)			
Serum albumin ≤4 g/dL	0.003	7.07 (1.95–25.6)	0.003
Simultaneous colorectal resection	0.002	–	NS
Group Cx-BV or Cx-OI and chemotherapy duration >150 days	0.01	5.42 (1.55–19.0)	0.008
Intraoperative blood loss >500 ml	0.015	–	NS
Operation time >300 min	0.018	–	NS
Bile leakage Grade ≥ B			
Diabetes mellitus (+)	0.001	–	NS
Initially unresectable	0.011	–	NS
Group Cx-BV or Cx-OI and chemotherapy duration >150 days	0.039	–	NS
Tumor size >5 cm	0.003	–	NS
Operation time >300 min	0.036	–	NS
CD ≥ IIIa			
Simultaneous colorectal resection	0.017	–	NS
Tumor size >5 cm	<0.001	–	NS
Major hepatectomy	0.013	–	NS

Group Cx-BV: fluoropyrimidine-based regimens + oxaliplatin or irinotecan + BV; Group Cx-OI: fluoropyrimidine-based regimens + oxaliplatin or irinotecan

BV bevacizumab, *Cx* chemotherapy, *CD ≥ I* complications of Clavien–Dindo grade I or higher, *CD ≥ IIIa* complications of Clavien–Dindo grade IIIa or higher, *NS* not significant

postoperative morbidity or mortality in patients who underwent preoperative chemotherapy [31–33]. This discrepancy may have been partly derived from the inconsistent definition of postoperative complications. Indeed, most of the previous reports included all kinds of postoperative complications in the analysis without stratifying their severity [9, 10, 18, 30].

In this study, we classified the postoperative complications according to the grading system and investigated whether the preoperative chemotherapy had any correlation with the occurrence of clinically relevant complications. We found that the rates of clinically relevant severe complications (bile leakage Grade ≥ B and CD ≥ IIIa) were similar between Groups NCx and Cx, and among Groups Cx-BV, Cx-OI, and Cx-M. Additionally, chemotherapy-related factors were not associated with the occurrence of severe complications in multivariate analysis. To the best of our knowledge, this is the first Asian report demonstrating that Cx-BV was not associated with high morbidity rates compared with other regimens. In addition, our short-term outcome was better with zero post-hepatectomy liver failure and mortality compared with others, for which the rates of postoperative liver failure and mortality in patients who underwent preoperative chemotherapy were 6–20 % and 1–4 %, respectively [9, 14, 33].

There are several possible explanations for the low rates of severe postoperative complications in our study. First, major hepatectomy was not frequently conducted in our series, even for patients with multiple CRLMs (only 18 %). In addition, PTPE was performed when the FLR volume was anticipated to be small. Our operative strategy was to choose multiple partial hepatectomies if possible, rather than major hepatectomy and to preserve sufficient FLR volume. This is because it is not the resected liver volume but the adequate surgical margin that contributes to improved postoperative prognosis [6, 34, 35]. This strategy may have contributed to prevention of liver failure. Second, 64 % of patients who underwent oxaliplatin-based chemotherapy also received BV, which has a protective effect on SOS [13, 14]. As a result, pathologically confirmed severe SOS was rare in our series (4 %), although 51 % of Group Cx received oxaliplatin-containing regimens. Our results are comparable with other studies, in which the incidence of moderate to severe SOS after chemotherapy including oxaliplatin and BV was 8 % [13].

In previous studies, short intervals between the final chemotherapy session and hepatectomy were reported to be associated with high incidence of postoperative complications. Intervals of ≥14 days after chemotherapy [36, 37] and >35 days after BV are recommended before hepatectomy [5, 15, 38, 39]. In our study, the median interval between the final chemotherapy session and hepatectomy was 56 days (≥15 days) and only 7 % of the patients underwent hepatectomy within 28 days after the final

chemotherapy. This may be another reason why postoperative complications were not frequently observed in our study.

With regard to the association between chemotherapy duration and postoperative complications, >150 days of chemotherapy including oxaliplatin or irinotecan was an independent predictive factor of CD $\geq$ I in our study. This result was similar to previous studies, in which six, nine, and 12 cycles of preoperative chemotherapy were shown to be associated with increased SOS or postoperative complications including liver insufficiency [11, 14, 18, 30]. However, prolonged chemotherapy was not an independent predictive factor of severe complications (bile leakage Grade $\geq$ B and CD $\geq$ IIIa) in this study. Thus, we consider that a long history of chemotherapy itself is not a contraindication for hepatectomy, although caution should be taken to avoid complications.

This study had several limitations. This was a retrospective study with several missing clinical data. Additionally, there was heterogeneity in the regimens and duration of preoperative chemotherapy. However, these represented the most practical data during the study period including all the consecutive patients in our hospital. Finally, the pathological examination of nontumorous liver parenchyma was sometimes difficult because of the small amount of specimen, and the severity of chemotherapy-related liver injury was not graded pathologically. This may be related to the low rate of SOS in our study compared with previous reports (18.9–60.5 % in patients who underwent oxaliplatin-based chemotherapy) [10, 11, 13]. However, a low rate of SOS (10 %) has been reported recently, irrespective of chemotherapy regimens [32].

In conclusion, hepatectomy can be performed safely without increasing morbidity or mortality even in patients who undergo preoperative chemotherapy including oxaliplatin, irinotecan, and bevacizumab, if the patients fulfill the conventional operative indication criteria.

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Compliance with ethical standards

Conflicts of interest None of the authors have personal conflicts of interest associated with the publication of this article.

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